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# OBSERVATIONS ON THE COURSE OF ALLERGIC RHINITIS AND BRONCHIAL ASTHMA IN RAGWEED-SENSITIVE SUBJECTS

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MANY of the basic problems in allergic disease are unsolved. The existence of a dose-response relationship to aeroallergens is not established. Investigation is hampered by failure to produce an allergic disease in experimental animals which is akin to the extrinsic airborne protein sensitization in man. Study of the course of allergic rhinitis and bronchial asthma in man is complicated by variability of environment and a myriad of factors such as diet, fatigue, emotions, temperature, and humidity which contribute to the "total allergic load"[7] but which are not defined quantitatively. In addition, the laws governing pollen distribution are unknown. A five-year study at the University of Michigan, by physicians, botanists, meteorologists, and engineers is contemplated in an effort to contribute to a better understanding of some of the factors involved in allergic responses to airborne allergens. The initial clinical phase of this investigation is the subject of this report.

In a previous investigation into the course of pollenosis,[9] inability to control the environment of subjects was thought to contribute to the inconclusive nature of the results. To achieve better environmental control, and at the same time to observe the patients more frequently, this study was pursued during August and September, 1955, at the State Prison of Southern Michigan. Thirteen inmates with ragweed sensitivity of clinical significance were observed and examined daily. The availability of the subjects and the similarity of environment of these individuals, confined in one small area, eating the same food, and rigorously adhering to similar schedules of activity each day, afforded opportunity to follow

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TABLE I.

| Subject | Age in Years | Manifestation of Disease (by history) | Skin Test to Ragweed Antigen* | | Time of Daily Visit |
|---|---|---|---|---|---|
| | | | Scratch | Intracutaneous | |
| 1. G. R. | 39 | Rhinitis | 0 | 2+ | 8:30 A.M. |
| 2. J. R. | 32 | Rhinitis and asthma | 3+ | | 8:55 |
| 3. C. S. | 64 | Rhinitis and asthma | 4+ | | 9:20 |
| 4. A. B. | 34 | Rhinitis and asthma | 0 | 3+ | 9:45 |
| 5. J. S. | 42 | Rhinitis and asthma | 2+ | | 10:35 |
| 6. E. J. | 29 | Rhinitis and asthma | 3+ | | 11:00 |
| 7. L. B. | 35 | Rhinitis and asthma | 3+ | | 1:00 P.M. |
| 8. L. C. | 27 | Rhinitis | 3+ | | 1:25 |
| 9. R. H. | 36 | Rhinitis | 4+ | | 1:50 |
| 10. S. R. | 50 | Rhinitis | 4+ | | 2:40 |
| 11. E. M. | 26 | Rhinitis and asthma | 2+ | 4+ | 3:05 |
| 12. L. F. | 27 | Rhinitis | 3+ | | 3:30 |
| 13. W. W. | 41 | Rhinitis | 3+ | | 3:55 |

*Intracutaneous tests performed only where results of scratch testing were negative or questionable.

the course of allergic disease more closely than is usually possible. Further, none of the subjects was receiving hyposensitization, and the manifestations of allergic disease were, therefore, not masked by the presence of artificially induced blocking antibodies.

## METHODS

From volunteer inmates with allergic rhinitis or bronchial asthma, a group of individuals who experienced symptoms primarily or exclusively in August and September was selected. Only those with a positive skin test to ragweed antigen were considered. The final selection of subjects was made after a complete allergic and general medical history, thorough physical examination, inspection of prison health records and x-rays, and skin testing to extract of mixed fungus, house dust, and pollen of mixed weeds, mixed grasses, and mixed trees.[14] Final selection of subjects was made on consideration of all information obtained. Of particular importance was evidence of rhinitis or asthma during August and September of previous years as recorded on the prison health records.

After subjects were selected, a schedule was arranged whereby each individual would be seen at the same time each day. Table I records the pertinent data. At each daily visit, vital signs were noted, the conjunctivae, nasal membranes, pharynx, and chest were examined, and the symptoms experienced over the previous twenty-four hours were reviewed with each subject. These symptoms were recorded on a card which was carried by each subject and exchanged for a new card at each examination. An index of symptoms was calculated for each subject and collectively for the group as previously described.[9] The one second and total vital capacity were determined, employing a Gaensler-Collins Vitalometer. In addition to these daily data, periodic eosinophil counts were obtained. Daily gravity counts were determined for ragweed pollen,[5] the sampler being located on the roof of a high building within the prison walls, and not far from the center of activity. A volumetric apparatus was also employed

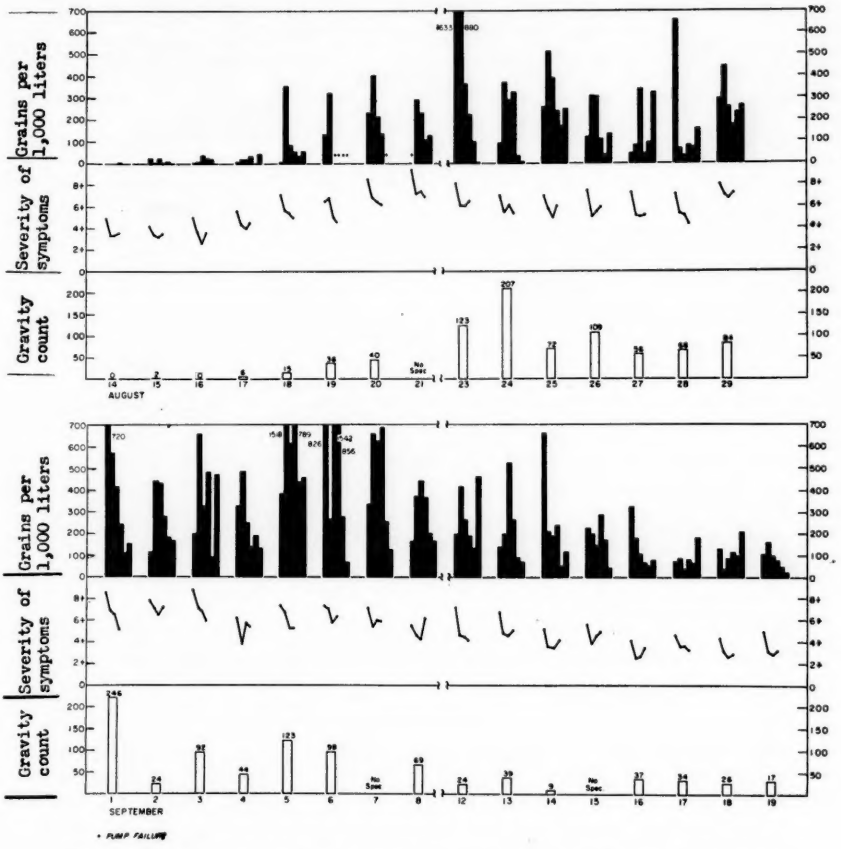


Fig. 1. Solid vertical bar graphs record ragween pollen grains per 1000 liters of air sampled during thirty-minute periods. The initial value each day is the 8:00-8:30 a.m. determination and subsequent portions of each day's solid bar graph represent values obtained at 4-hour intervals. Data are expressed in this manner so each daily profile corresponds to a gravity count (expressed as open bar graph). Severity of symptoms, expressed on an arbitrary scale from 0 to 10+, is also recorded as a broken line segment connecting the four points daily representing 8:00 a.m., noon, 4:00 p.m., and 8:00 p.m. estimations. Dates are indicated on the abscissa.

to obtain the concentration of ragweed pollen six times in each twenty-four-hour period. The construction of this apparatus and the method of expressing results has been described in detail elsewhere.[3]

A survey of the prison grounds and adjacent areas was made for distribution and concentration of dwarf and giant ragweed plants. Cell blocks were inspected and found to be tidy and clean, in accordance with routine prison regulations. A minimum of simple wood furniture was present in

TABLE II. LOWER RESPIRATORY TRACT SYMPTOMS AND SIGNS IN SIX SUBJECTS WITH ALLERGIC RHINITIS

| Subject | Month | Symptoms | | | | Signs |
|---|---|---|---|---|---|---|
| | | Wheezing | Cough | Shortness of Breath | Chest Tightness | |
| L. C. | Aug. | 14 | — | 19, 20, 21, 22, 23, 24 | 14 | — |
| | Sept. | — | 9 | — | — | 6 Scattered rales at lung bases |
| G. R. | Aug. | — | — | — | — | — |
| | Sept. | 12, 13 | — | — | 12 | 9 Expiratory wheeze |
| S. R. | Aug. | — | 13, 15, 19-25, 29, 30, 31 | — | 16, 18, 21, 27, 29, 31 | — |
| | Sept. | 8, 11 | 1, 2, 4, 5, 8-12, 17, 19-22 | — | 1, 6 | — |
| W. W. | Aug. | — | — | — | — | — |
| | Sept. | — | 2, 3, 13-15 | — | — | 2, 13 Coarse rhonchi |
| R. H. | Aug. | — | — | — | — | 22, 23 Musical rales |
| | Sept. | — | — | — | 10 | — |
| L. F. | Aug. | — | 21, 22 | 18-22, 26, 29, 30 | — | — |
| | Sept. | — | 6 | — | — | — |

Number refers to date symptom was recorded or sign was observed. For example, subject G. R. reported no symptoms and no abnormalities were noted on daily examination in August. However, in September he complained of wheezing on the 12th and 13th, and chest tightness on the 12th. On September 9, expiratory wheezes were noted on physical examination.

the cells. No rugs or curtains were permitted. In order to minimize exposure to antigenic dust, plastic pillow and mattress covers were used.

## RESULTS

One patient (not included in Table I) was excluded from the study because of pleuritis which was thought to interfere with vital capacity determinations. The remainder of the group, thirteen subjects in all (Table I), was free of illness other than allergic disease during the period studied. No significant temperature or pulse changes were noted.

Figure 1 records the daily gravity count of ragweed pollen, the daily pollen profiles, and the fluctuation of index of symptoms of the entire group during the waking hours. To some degree, the severity of symptoms may have been reduced by antihistamines or quadrinal which was taken daily throughout the season by some individuals, for long periods of time by others, and not at all by others. Except for subcutaneous epinephrine, administered rarely when asthma was severe, patients did not receive casual medication. Either they were on a roster to receive the medication three times daily regardless of symptoms, or they did not receive medications. Consequently, it was felt that fluctuations in symptoms were not likely to be attributed in any large degree to medications received.

Some patients experienced mild allergic symptoms prior to the appearance of ragweed pollen in the air, possibly due to dust and other aero-

allergens. As ragweed pollen appeared in the air and its concentration increased from August 14 to 21, as measured by both gravity slides and volumetric sampling, there was a steady increase in severity of symptoms. As has been reported previously,[9] there does not appear to be a temporal

TABLE III.
VITAL CAPACITY FLUCTUATIONS

| Bronchial Asthma | | Allergic Rhinitis | |
|---|---|---|---|
| J. R. | $\frac{31\text{-}43}{37\text{-}48} = \frac{12}{11}$ | L. C. | $\frac{38\text{-}51}{40\text{-}55} = \frac{13}{15}$ |
| C. S. | $\frac{12\text{-}35}{32\text{-}44} = \frac{23}{12}$ | R. H. | $\frac{33\text{-}44}{39\text{-}52} = \frac{11}{13}$ |
| A. B. | $\frac{13\text{-}39}{21\text{-}45} = \frac{26}{24}$ | S. R. | $\frac{30\text{-}40}{34\text{-}44} = \frac{10}{10}$ |
| J. S. | $\frac{24\text{-}35}{25\text{-}41} = \frac{11}{16}$ | L. F. | $\frac{39\text{-}48}{40\text{-}50} = \frac{9}{10}$ |
| E. J. | $\frac{20\text{-}44}{24\text{-}58} = \frac{24}{34}$ | W. W. | $\frac{32\text{-}36}{35\text{-}38} = \frac{4}{3}$ |
| L. B. | $\frac{34\text{-}40}{37\text{-}48} = \frac{6}{11}$ | G. R. | $\frac{37\text{-}42}{40\text{-}46} = \frac{5}{6}$ |
| E. M. | $\frac{30\text{-}44}{36\text{-}48} = \frac{14}{12}$ | | |

The numerator records the lowest and highest values of the one-second vital capacity in hundreds of cubic centimeters. The denominator expresses the lowest and highest values of the total vital capacity in hundreds of cubic centimeters. The range over which these values fluctuate is indicated as the difference between the highest and lowest value. For example, the lowest one-second vital capacity recorded on A. B. during the study was 1300 cc. The highest vital capacity recorded on A. B. was 3900 cc. Hence, there was a 2600 cc. range over which the one-second vital capacity fluctuated during the course of the study.

relationship between fluctuations of pollen concentration and fluctuations in subjective evaluation of symptoms. On numerous occasions, high concentrations of ragweed pollen failed to produce the expected increase in severity of symptoms in our group of ragweed sensitive individuals.

Seven patients gave a history of both allergic rhinitis and bronchial asthma, and objective evidence for both conditions was present during the course of the investigation. One subject (R.H.) denied asthma, but on two occasions, August 22 and August 23, 1955, moderately loud musical râles were heard on expiration. Five subjects who denied asthma in their initial history either reported definite chest symptoms such as cough, unusual shortness of breath, wheezing, or tightness of the chest, or they were found to have wheezing or rhonchi on physical examination. The pulmonary findings in allergic rhinitis patients are summarized in Table II.

The range of fluctuation of daily one-second and total vital capacities during the interval from August 15 to September 22 for each patient is recorded in Table III. With only slight overlap, it appears that the fluctuations of vital capacity in patients with asthma are, as expected,

FIG. 2

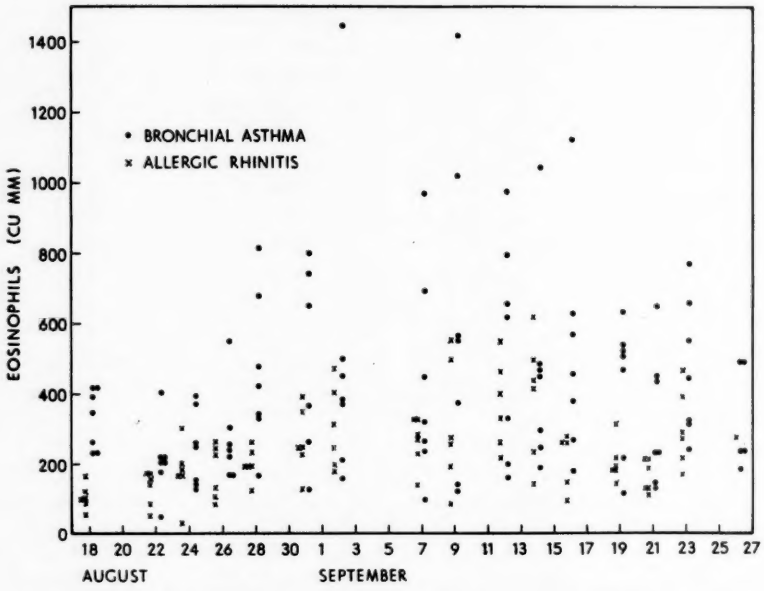


Fig. 2. Eosinophil counts, expressed as eosinophils per cubic millimeter of blood. Dates of obtaining the counts are recorded on the abscissa. Each solid dot represents the eosinophil count of a patient with bronchial asthma. Each x represents the eosinophil count of a patient with allergic rhinitis.

greater than the fluctuations in allergic rhinitis. We wish to call attention to the wide range over which measurements fluctuate in the group whose illness was originally thought to be confined to the upper respiratory tract. In neither group of patients did a consistent pattern appear; severe reduction of vital capacity might be found in some individuals while others would show little or no reduction on any single day. In the case of one asthmatic patient, as will be described in more detail below, continuous bronchodilator and expectorant therapy until September 6 may have prevented the development of symptoms. This was not true in other patients on maintenance therapy, who, nevertheless, experienced moderate to severe symptoms during the course of the study.

The eosinophil counts are plotted on Figure 2, and are expressed in eosinophils per cubic millimeter. The values are plotted above the dates when counts were obtained. Values from allergic rhinitis patients are plotted as crosses, and values from bronchial asthma patients are plotted

as closed circles. If 450 eosinophils per cubic millimeter is accepted as the upper limit of normal,[1] six of seven asthmatic and one of six allergic rhinitis patients demonstrated a significant eosinophilia on one or more occasions. The one individual (R.H.) in the allergic rhinitis group who had an eosinophilia on four occasions, reaching 621 per cubic millimeter on September 14, is the individual who was observed to have musical râles on examination, although he denied having asthma.

Since the prison yard and adjacent grounds are well cultivated, it was anticipated that little ragweed would be found within or in close proximity to the prison compound. A botanical survey, however, disclosed patches of ragweed within the prison, primarily in recreation areas, and extensive growth in several locations just outside the prison wall.

The vital capacity fluctuations, medications, eosinophil counts, and subjective symptoms of two asthmatic subjects are shown on Figure 3. The course of these individuals is described in detail because of the interesting effect of medication on the course of their illness and because we wish to discuss the eosinophilia in relation to the asthma.

A.B. had experienced severe asthma in previous years and had obtained relief with an aerosolized bronchodilator. Because this medication was not permitted in prison, and because the patient was fearful and apprehensive, he was maintained on one tablet of Quadrinal® three times daily prior to and during the initial weeks of the ragweed season. E.J. received no medication prior to the development of severe asthma. With the rise of ragweed pollen concentration in mid-August, A.B. experienced only minimal nasal symptoms, and no subjective or objective evidence of asthma. E.J., however, reported nasal symptoms which increased with rise in the ragweed concentration. He experienced slight cough on August 21 and on August 22 the vital capacity had fallen to 20/28. At this time the eosinophil count was in the normal range. The following day, bilateral high-pitched musical râles were heard. Except for .5 ml of 1:1000 aqueous epinephrine after the examination of August 22, no medication was taken prior to August 25. Although A.B. was almost completely free of both subjective and objective symptoms, and E.J. experienced little asthma between August 29 and September 5, both individuals had elevated blood eosinophil counts during this period.

Medication was discontinued by E.J. on September 8, and although a decrease of one-second vital capacity for six days and total vital capacity for five days was recorded, and eosinophilia persisted, the patient experienced only daily mild cough and occasional mild dyspnea and wheezing for the remainder of the season.

A.B. experienced only minimal nasal symptoms and cough prior to September 6, and was free of objective evidence of asthma except for a localized area of musical râles at the right base posteriorly during forced expiration with the aid of external compression on August 31. However, eosinophilia was found on and after August 29. The patient willingly

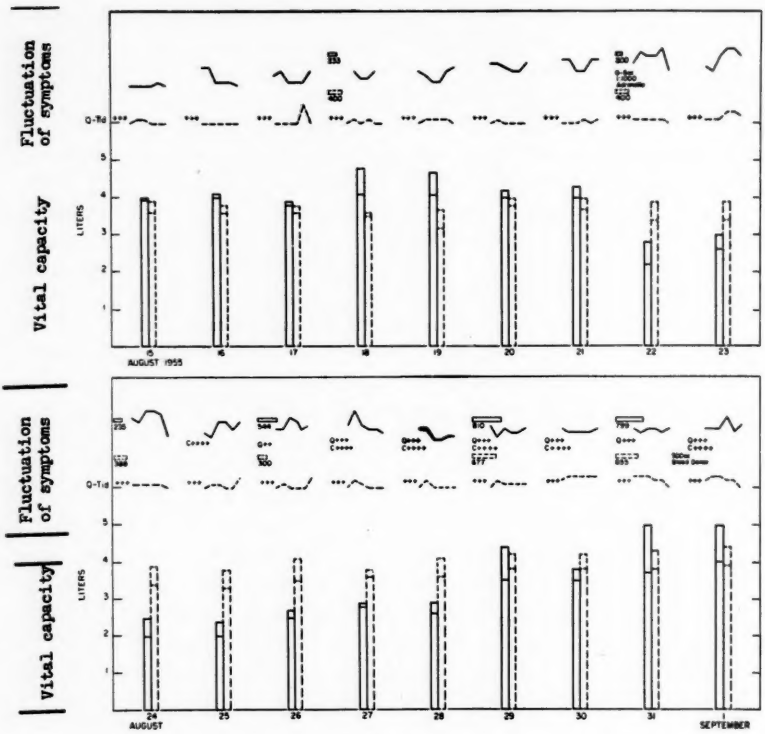


Fig. 3a

Fig. 3 (a and b) Solid lines and bar graphs refer to subject E.J., dotted lines and bar graphs to A.B. One-second and total vital capacities, expressed in liters, are plotted as vertical bar graphs. Horizontal line segments represent fluctuation of index of symptoms. Horizontal bar graph segments and accompanying numerical values record eosinophils per cubic millimeter. Medications are also recorded (Q = Quadrinal®, C = chlorprophenypyridamine maleate), each + representing one tablet; +++ indicates one tablet taken three times daily, at approximately eight-hour intervals. Dates of observation are plotted on the abscissa.

discontinued medication on September 6, and the following day cough, wheezing, and dyspnea were reported and bilateral inspiratory and expiratory râles were heard. A precipitous fall in vital capacity did not occur until September 12, however, and the patient resumed medication on the following day. After September 14, only occasional mild wheezing and cough was reported and no objective evidence of asthma was recorded.

## DISCUSSION

We believe much is to be learned by daily observation of a limited number of subjects under environmental control as rigorous as possible. Only a small number of intensive investigations over a prolonged period

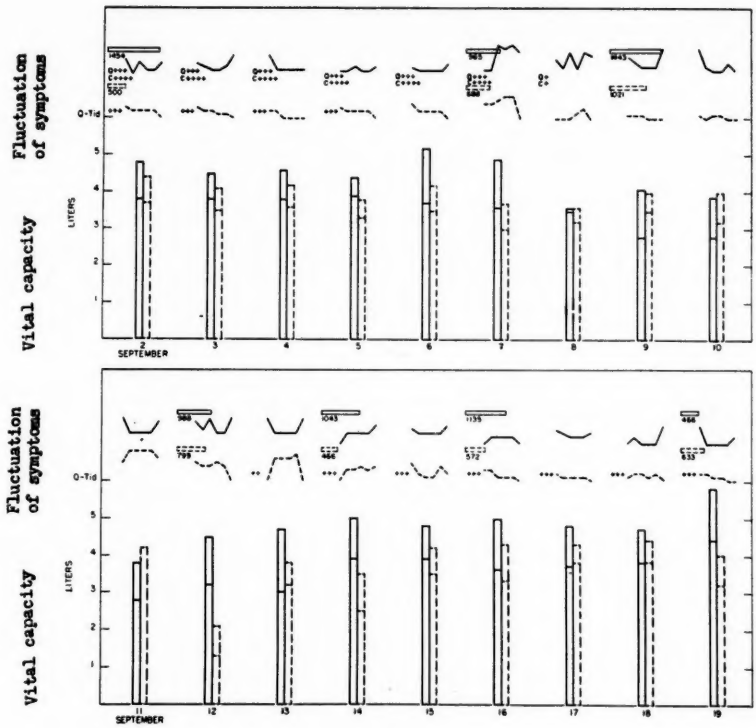


Fig. 3b
*(For legend, see Page 374)*

have been reported. Even among the most outstanding of these,[2,6,12,16] daily objective evaluation was not possible or thought essential.

The increase of severity of symptoms in the first week of the season roughly paralleling the rise in concentration of ragweed pollen would suggest the existence of some kind of a dose-response relationship. The absence of any consistent similarity of fluctuation of symptoms and pollen concentration on any given day suggests that the method of sampling is unreliable, symptoms do not follow rapid fluctuations of pollen concentration, or perhaps fluctuations of pollen concentration at one location are in no way representative of fluctuations over a small area. Studies at the Engineering Research Institute of the University of Michigan in the last year[4] so far indicate the apparatus and procedure yield reliable results. These studies will continue, and in future investigation, continuous sampling over each four-hour period rather than thirty-minute sampling every four hours may yield results that correlate better with subjective evidence of severity of illness. Even more rigorous environmental control is contemplated in future investigations, with several

patients and a volumetric sampler confined to a small homogeneously ventilated environment. It became apparent that the environmental uniformity desired was not present when patches of ragweed plants were found in the areas to which the subjects had free access on several occasions daily. The existence and nature of a dose-response relationship between ragweed pollen and allergic rhinitis or bronchial asthma remains to be defined.

An eosinophilia above 450 per cubic millimeter in six of seven asthmatics and only one of six allergic rhinitis patients suggests systemic manifestations of asthma are more severe than in allergic rhinitis. The eosinophilia failed to correlate with other manifestations of the disease. One patient developed severe asthma and demonstrated reduction of the vital capacity prior to the appearance of significant eosinophilia, and later in the season his eosinophil count exceeded 1400, although his symptoms at that time were only mild and he was not receiving any medication. The minor degree of symptoms experienced by A.B. while on Quadrinal®, and the simultaneous development of an eosinophilia to a high level constitutes further evidence that underlying pathological processes are in action, in spite of symptomatic relief or control obtained with this medication. It will be noted that most asthmatic patients had eosinophil counts in the morning, and most allergic rhinitis patients had determinations in the afternoon. Although diurnal variations in eosinophil count have been reported, [10,13] they are probably not sufficient to account for the differences observed in our subjects. Daily eosinophil counts in the fasting state in both groups might yield interesting results.

Since Staehelin and Schultze used the vital capacity in asthma in 1912,[15] this test has been employed as an objective measure of the degree of respiratory embarrassment in bronchial asthma. The timed vital capacity constitutes a further modification thought to increase the significance of the results obtained.[8,11] In this study, both one-second and total values are recorded. The one-second value does not consistently appear to be any more indicative of subjective or objective impairment of ventilation than does the total vital capacity. We agree with Lowell, Schiller, and Lynch[12] that there is no consistent relationship between physical findings and changes in pulmonary function.

It is of interest to note a greater fluctuation of vital capacity in allergic rhinitis patients than we would expect, and this observation is in accord with the findings of Brown et al[2] who conclude that patients with uncomplicated hay fever and no history of bronchial asthma may frequently demonstrate a diminished vital capacity during their pollen seasons. It has also been demonstrated by Tuft[16] that some allergic rhinitis patients experience a decrease in breathing capacity during the pollen season.

We agree with Lowell, Schiller, and Lynch,[12] that ". . . no single criterion can serve as an adequate measure of the severity of bronchial asthma." It is our hope that as a result of intensive study of volunteer

subjects in an environment as completely controlled as possible, additional information relating to the pathogenesis of allergic rhinitis and bronchial asthma can be obtained. To this end, additional investigation is in progress.

## SUMMARY AND CONCLUSIONS

Careful frequent observations were made on six allergic rhinitis and seven bronchial asthma subjects. The following conclusions are suggested:

1. Early in the ragweed season, as the pollen concentration increases, patient's symptoms also increase. A relationship appears to exist between symptoms and the ragweed concentration as measured by the gravity counts. A relationship between symptoms and frequent volumetric counts over each twenty-four-hour period cannot be demonstrated.

2. Pulmonary symptoms or signs, sufficiently mild or infrequent to escape detection unless searched for carefully, can be uncovered or observed frequently in patients with allergic rhinitis.

3. Eosinophilia is common and reaches higher levels in patients with bronchial asthma than in patients with allergic rhinitis. The level of eosinophil concentration is not related to severity of symptoms. Development or persistence of eosinophilia can be observed while the subject is rendered or maintained asymptomatic with conservative drug therapy. This suggests that abnormal systemic processes may continue although their manifestations are not apparent.

## ACKNOWLEDGMENT

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*Submitted November 2, 1956*

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## ASTHMA

To the Editor of the Boston Medical and Surgical Journal.

Sir,—In the Journal of February 4 the question has been put forward by Querist, "Is excessive venery ever a cause of asthma?" As an exciting cause I should think it might be classed among the other many sources giving origin to the disease. The abuse of the venereal appetite is a more serious subject than many imagine, frequently destroying the individual in the act, and often times laying the foundation of serious structural lesion. It is particularly dangerous after surgical operations, inducing sudden and fatal hemorrhage. (In the last peninsular war numbers died from this cause.) Apoplexy sometimes occurs, especially if the stomach is distended with food. Celsus gives excellent advice, when warning us to avoid coition after meals or during the day. If I recollect aright, two cases are on record of rupture of the right auricle taking place during the act.

*As to its producing asthma, it might do so by deranging the powers of assimilation, causing a reflex irritation to be communicated through the eighth pair, the condition of the nervous system, more especially the nerves of respiration, giving the bronchial muscles unusual irritability.* Hence, I do not think that humoral or spasmodic asthma would be probable to occur in copulation. The lesion most likely to take place would be a *rupture of the air cells* by excessive or sudden dilatation, in fact *interlobular emphysema*, which if not extreme would be apt to subside spontaneously. I imagine the case cited by "Querist" as occurring in the act of coition to have been one not of asthma, but of this description.

Derry, N. H., February 12th, 1846. Yours respectfully,
N. M.

# USE OF NON-FLUSHING DOSES OF HISTAMINE IN THE TREATMENT OF FOREIGN PROTEIN TYPE REACTIONS

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THIS is a report of twenty-five cases of foreign protein type reactions treated with non-flushing doses of histamine with the technique of administration and a suggested mode of action.

The literature on the use of histamine in reactions of this type emphasizes that generalized flushing must be achieved to produce a favorable response. Since the criterion of flushing is absent in our series, a different modality of action will be offered.

Our interest in histamine treatment of foreign protein type reaction stems from a report of excellent results by Prince and Etter in 1950.[9] Shortly thereafter, a method of administration of histamine was suggested to this author by Dr. Herbert Rinkel. The use of this technique in a severe penicillin reaction yielded a most gratifying result.

We have since used the same method in many types of allergic conditions. These conditions were recently classified by Blue[3] "where the antigen-antibody reaction is not demonstrable." In the foreign protein type reactions the results have been consistently good. This observation seems quite compatible with reports by Prince and Etter[9] and Blue.[3] It seemed to us, therefore, that cases in this group could be presented most clearly and compared most readily with other published series.

The patients chosen for inclusion in this report were those seen during a period from June 21, 1951, to April 19, 1956, who had a foreign protein type injection or exposure less than one month before the onset of symptoms. The list of suspected offenders and their incidence are shown in Table I and the incidence of symptoms is listed in Table II.

The duration of symptoms before initiation of histamine treatment varied from one to seven days in nineteen cases. In the remainder the duration was nineteen days, twenty-six days, three weeks, four weeks, five weeks, and twelve weeks.

Thirteen of the cases had previous treatment with antihistaminics without improvement. One had also received ACTH and cortisone. One had treatment consisting of intravenous and intramuscular injections of unknown type, and eleven cases had no previous therapy for their reactions.

## TECHNIQUE OF ADMINISTRATION

Serial dilutions of one to five are made of a stock solution of histamine diphosphate 2.75 mgm per cc. Five dilutions of the original strength have sufficed for all the treatments we have administered. We use a system of labeling the dilutions which is similar to that originally

TABLE I. SUSPECTED OFFENDERS

| Agent | Incidence |
|---|---|
| Penicillin (admixture of streptomycin in some) | 18 |
| Tetanus Antitoxin—gas gangrene antiserum | 2 |
| Tetanus Antitoxin | 1 |
| Black widow spider bite antivenin | 1 |
| Procaine Penicillin and Tetanus antitoxin | 1 |
| Penicillin powder contact while dehorning cattle | 1 |
| Acthar Gel | 1 |

TABLE II. SYMPTOMS OF FOREIGN PROTEIN TYPE REACTION

| Symptom | Incidence |
|---|---|
| Generalized urticaria | 22 |
| Angioneurotic edema | 6 |
| Joint pain and swelling | 5 |
| Swelling and itching of palms and soles | 2 |
| Urticaria localized at site of injection of offending agent | 2 |
| Fever | 1 |

suggested by Rinkel.[6]* The stock solution is called the concentrate. The 1:5 dilution of the concentrate is No. 1. The 1:5 dilution of No. 1 is No. 2 and so on down to No. 5.

The steps of the technique are as follows: Starting with dilution No. 5, a 4 mm intradermal wheal is raised and ten minutes allowed to elapse. The desired reaction is at least a 7 mm wheal with a zone of erythema totaling about 25 mm or more. If no reaction occurs or there is less than a 7 mm whealing, the next strength is used and so continued till the desired reaction is obtained. When the reaction is obtained, treatment is begun with the solution just below in strength to the one that produced the reaction. Thus if No. 3 produced the reaction, treatment is begun with No. 4. The starting dose is 0.25 cc, followed by 0.35 cc and 0.45 cc at four-hour intervals always given in subcutaneous injections. In most cases the following day and on subsequent days one dose of 0.10 cc of the dilution producing the reaction is given. If symptoms are not completely controlled, the dose is given twice a day. The treatment is usually continued until symptoms have been controlled for two or three days.

In practice, Dilutions No. 4 and No. 3 are used immediately in testing. There have been no reactions below No. 4, and in only two cases was the reaction with No. 4. In the cases where this occurred, No. 3 should and did produce an over-reaction. However, since the amount of material deposited in the skin test is about 0.01 cc, this is equal to 0.25 cc of the No. 5 dilution. This can be assumed to represent also the first treatment dose. If there are no reactions, Nos. 2 and 1 are used and the same principles applied. Consequently, only fifteen to twenty-five minutes are required to complete the testing and give the first treatment.

*Since the publication of Rinkel's article, his numbering system has been changed and corresponds with that used in this paper.

Seven of the successfully treated patients were hospitalized. Six of them were considered so severely affected by the reaction that hospitalization was considered mandatory by the referring physician. One patient was hospitalized for her convenience. Seventeen were treated in the office. In several instances when it was inconvenient to return to the office or after office hours, it was a simple matter to teach the patient or a member of his family to give the injections at home.

TABLE III. HISTAMINE BASE USED

| Dilutions Used | Average Daily Dose of Histamine Base | Number of Cases |
|---|---|---|
| 5 and 4 | 0.00035 mg | 2 |
| 4 and 3 | 0.0020 mg | 8 |
| 3 and 2 | 0.010 mg | 12 |
| 2 and 1 | 0.045 mg | 3 |

It is of value to visualize the dose of histamine base used in these treatments. This is shown in Table III.

It will be noted that the highest dosage used, or 0.045 mg, closely approached the starting dose for titration for the intradermal flushing dose used by Prince and Etter.[9] It is likely that these patients would have required much larger doses to flush and probably would have been in the intravenous ranges. In the intravenous method 1 mg or more is generally used per treatment.

## RESULTS

The result in twenty-four cases was considered successful. In twenty-three cases there was improvement in one day and complete recovery in one to four days. In one case the improvement seemed to lag and the patient was retested on the third day and found to require the next higher strength dilution. He was well three days later. This case was peculiar in that all the intradermal tests produced only a narrow zone of erythema of two or three mm. One of the twenty-four cases, who had had symptoms for five weeks before treatment, was slower to respond and had two recurrences, but was controlled within a period of four to five days on each occasion.

One case appeared to be unresponsive to this treatment. This was a twenty-four-year-old married woman who was delivered of her third baby in three years at term on December 28, 1952. She had an injection of procaine penicillin on about November 20, 1952, for a cold. Urticaria began one month later. After delivery, on December 30, she had a blood transfusion which was followed by a marked exacerbation of urticaria, joint pain and swelling. These symptoms persisted and she was referred to our office for treatment on January 8, 1953. Previous to that date, treatment had consisted of Pyribenzamine®. Treatment was begun on No.

4 dilution and continued in the usual manner. There was some evidence of improvement in forty-eight hours, but on January 11 the urticaria became worse. She was given Acthar Gel 40 units intramuscularly in the evening of January 12 and again on the morning of January 13. Later on that day she was admitted to the hospital because the urticaria was still not relieved, and she was given 10 units of ACTH in 1000 cc Ringer-lactate solution intravenously from 5 p.m. to 11 p.m. She was improved and left the hospital on January 14. On January 15 she left to stay at her parents' home in another state. She reported later that the urticaria continued for three months. She had no further medical care, but took nerve tablets and rested frequently and was able to tolerate the urticaria fairly well.

Psychogenic factors or the blood transfusion may have complicated the picture in this case. The long interval, four weeks, between the penicillin exposure and the onset of symptoms cast some doubt on the etiology.

Another factor not investigated in this case and the one with recurrent attacks of urticaria is the synergistic effect of yeast-containing foods and penicillin reactions. This concept, suggested by Dr. Rinkel in a recent personal communication received since the completion of this study, is mentioned in this paper with his permission. He has found that the ingestion of yeast-containing food has great import in a limited number of penicillin sensitizations.

## DISCUSSION

In our opinion, the results in the twenty-five cases treated by the non-flushing method appear to parallel closely those reported by Prince and Etter, and Blue. A study to compare results of our method and the flushing methods would be of value. This is a future objective.

Two advantages of the method presented are the simplicity of the technique and a minimum of discomfort to the patient.

In none of our cases was generalized flushing experienced and the level of dosage is far below that required for flushing. Apparently, sub-flushing doses have proven ineffective in the experience of Prince and Etter,[9] and Blue.[3] It appears, therefore, the dosages as arrived at by Rinkel's technique, which are far below that required for flushing, represent another level capable of producing relief of symptoms from foreign protein type reactions.

It appears that some mechanism other than capillary dilatation is responsible for the effectiveness of this method of treatment. One suggestion is that an enzyme system is stimulated to suppress the urticarial and other manifestations of these reactions by re-establishing a normal balance of histamine in the affected tissues.

Best and McHenry[1] demonstrated in 1930 that an enzyme active upon histamine exists in animal tissues and that it destroys histamine *in vitro;* they named this substance histaminase. They were never able to demon-

strate this activity *in vivo*. In the ensuing years there was considerable enthusiasm for the use of extracts containing this enzyme for treatment of allergic conditions, and it was commercially available under the trade name of Torantil from The Winthrop Chemical Company.

In 1946 Feinberg reviewed the literature on histaminase, as a therapeutic agent and found little evidence of any value.[6] This author noted no articles in the literature on its therapeutic use since that time. Winthrop is still marketing Torantil® and apparently it is still in use.

In 1949 Carlsten and his co-workers at the University of Lund Institute of Physiology in Sweden demonstrated that in the dog the thoracic duct lymph histaminolytic activity was more than thirty times greater than that of the animal's plasma.[4] They also showed, *in vivo*, that intralymphatically administered histamine was inactivated at a high rate. They tested the histaminolytic agent in this lymph and found it to be biochemically similar to histaminase.[5] They determined that it originated from the richly supplied tissues of the kidney and gut. Then they demonstrated that in animals there was an abrupt rise in the histaminolytic activity in thoracic duct lymph within a few hours after bilateral adrenalectomy, and this rise was sustained up to twenty-four hours.

In 1953 Haeger and his co-workers of the same institute demonstrated a similar rise in hypophysectomized cats.[8] They administered ACTH to these animals and restored the histaminolytic levels to normal.

They concluded that this hormone is necessary to retain histaminase in depots in the kidney and gut, and that the absence of the hormone results in the escape of histaminase from the depots and its dissipation.

Another suggestion might be that the rise in histaminolytic level is actually a compensatory mechanism to inactivate that portion of histamine in the tissues which is normally neutralized by the hormone.

In this country, Dragstedt and his co-workers[7] in 1955 report results similar to those of the Swedish workers with slight variations in similar experiments on dogs. Partially confirming Carlsten's and Haeger's work, they also showed a marked transient rise in histaminolytic activity of the thoracic duct lymph when they produced a spontaneous and precipitous fall in blood pressure, simulating shock in these animals.

It would appear that studies of the influence of flushing and non-flushing doses of histamine on the level of histaminase in the thoracic duct lymph of animals might prove significant.

## SUMMARY

Twenty-five cases of foreign protein type reactions have been treated with a new non-flushing dose of histamine. The dose depended on the reaction to intradermally tested serial dilutions of histamine diphosphate. The results appeared to be excellent in twenty-four cases.

The possibility that a histaminolytic enzyme system is an important factor in the mechanism is suggested.

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*Submitted December 20, 1956*

## BEQUEST TO THE ACADEMIC YOUTH OF HIS COUNTRY

What shall I wish for the young students of my country? First of all sequence, consequence, and again consequence. In gaining knowledge you must accustom yourself to the strictest sequence. You must be familiar with the very groundwork of science before you try to climb the heights. Never start on the "next" until you have mastered the "previous." Do not try to conceal the shortcomings of your knowledge by guesses and hypotheses. Accustom yourselves to the roughest and simplest scientific tools. Perfect as the wing of a bird may be, it will never enable the bird to fly if unsupported by the air. Facts are the air of science. Without them the man of science can never rise. Without them your theories are vein surmises. But while you are studying, observing, experimenting, do not remain content with the surface of things. Do not become a mere recorder of facts, but try to penetrate the mystery of their origin. Seek obstinately for the laws that govern them. And then—modesty. Never think you know all. Though others may flatter you, retain the courage to say, "I am ignorant." Never be proud. And lastly, science must be your passion. Remember that science claims a man's whole life. Had he two lives they would not suffice. Science demands an undivided allegiance from its followers. In your work and in your research, there must always be passion.—IVAN PAVLOV (1849-1936).

# ALLERGY IN THE FUTURE

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IT IS INDEED an honor to be invited to speak before you. The officers and members of the American Academy of Allergy send their greetings and best wishes for a successful meeting.

Perhaps the title of my message today should be changed from "Allergy in the Future" to "Alice-in-Wonderland Allergy," as she looks and then walks through the mirror into fantasyland. Maybe a better title might be, "Arbesman in Allergyland," as I hope to look into the mirror of allergy, and see ourselves, and then walk through the mirror and speculate (or perhaps hope) for the future! "The time has come," as the Walrus said, "to speak of many things."

As you know, for the past several years it has been the custom of the two national allergy societies to invite the respective presidents to address each other's organization. This is but one little point that draws our two groups closer and closer together. We each have similar aims: the disseminating of knowledge through meetings, research, and writing in allergy; to better educate ourselves, our fellow practitioners, and the public, as well as undergraduate and graduate medical students in this very broad field of hypersensitivity, so that we may better understand the complexities of our specialty, and thus better treat and help our patients. This is not just peaceful coexistence, but rather close cooperation and unity.

Our two national organizations have had close cooperation in many activities. To mention a few: The American Foundation for Allergic Diseases, The International Association of Allergology, Certification, Section on Allergy of the A.M.A., and, finally, but not least, the Committee on Amalgamation.

It is not my purpose here, today, to discuss the "pro's and con's" of amalgamation of our two groups, but there are many excellent points to having one organization with one meeting, one journal, and a united allergy front and, also, if I may be so bold to state, only one amount of yearly dues. However, there are, likewise, many factors that indicate that two organizations in one field are better. The arguments in favor of this are that it keeps both groups on their toes (competition is the spice of life), it allows those members interested in allergy to choose their own meeting place each year, and also the type of program they wish to attend, and last, but not least, it allows more members to have

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Dr. Arbesman is immediate Past President of the American Academy of Allergy.

a chance to participate in the functions and workings of two organizations rather than one.

The joint Committee on Amalgamation has been studying these many arguments and considerably more obstacles which must be overcome. The project for amalgamation is not dead. (You know it took many years for the two parent societies of the American Academy of Allergy to get together.) This all takes time.

(It is timely to mention that the International Association of Allergology is having its next Congress in Paris, France, in October, 1958. A very excellent scientific program and social program is planned. You are all members through the fact that the College is one of the participating societies. It should be lots of fun!)

The same arguments for certification in allergy could be brought out today—but I believe we are making progress both in possible amalgamation and certification. Time will tell. These are some of the items for allergy in the future! Although I have no crystal ball, we will probably some day have one large allergy organization with several divisions such as immunochemistry, botany, pure research, clinical and laboratory sections. These latter sections could then be further subdivided into internal medicine, pediatrics, dermatology, otorhinolaryngology, and ophthalmology. It is hoped that with certification in allergy within the framework of organized medicine (The American Medical Association), we will have allergy departments and services in the hospitals and medical schools which will give our specialty greater stature and its rightful place in medicine.

In certain respects we have already met some of these points. Allergy has been making great strides in both the educational and clinical fields. The postgraduate courses held each year at the time of the two national societies' meetings, the frequent postgraduate courses at county and state medical societies, the formation of more state allergy sections, the many postgraduate courses at various medical schools and centers throughout the country, the allergy courses of the American College of Physicians, and the section on allergy of the pediatric group: All of these sessions are well attended. The medical profession is hungry for knowledge in allergy.

At each of the Sessions on Allergy of the American Medical Association in the past several years there has been an excellent attendance. There were over twenty-five abstracts submitted for presentation at the Session on Allergy this year, but unfortunately, there was only time available for nine or ten papers. Hence, many good papers had to be refused. It was very difficult for the program committee to choose among these manuscripts, but it was felt that topics about which we are all more or less in accord should be presented at this type of meeting. We would have no difficulty in preparing for a section, which is three half days instead of one-half day. I feel that we will have a Section on Allergy of the American Medical Association within the next few years. Application for such a Section is now under consideration.

In addition to this postgraduate education, more opportunities are available at the undergraduate and graduate levels in allergy. There is more time devoted in many schools to the basic immunologic aspects of hypersensitivity and to clinical allergy. There are also an increasing number of approved and well-regulated allergy clinics, established residencies and fellowships, textbooks, and, of course, our medical journals.

An excellent survey of allergy education was made by the American Foundation for Allergic Diseases and published *in toto* in the ANNALS during the past year. As this survey indicates, we are still a long way from having satisfactory training programs. We will need the utmost cooperation with our medical colleagues in associated fields.

Are we, as allergists, prepared to accept these added responsibilities? Why do so many of our colleagues scoff at allergy, ridicule us, and find the field of allergy so bewildering and mystifying?

Certainly, extravagant claims and unusual procedures have brought justifiable criticism on our specialty. We have no real standardization in allergy. Even the classification of various types of allergic syndromes cannot be agreed upon. In the past year, a Committee on Nomenclature of the Academy was asked to study and report back a standard nomenclature for one condition, namely, bronchial asthma. So far, there have been as many divergent opinions as there have been members of this committee. Multiply this number by the various allergic conditions and the number of people interested in this field and you can readily see that we are a Tower of Babel. We don't even talk the same language among ourselves—so how can our colleagues outside the specialty understand us.

You all realize as well as I the need for standardization of extracts, standardization of techniques in preparation of extracts and their potency, standardization of skin tests—the amount and concentration to use, the number of tests to employ—whether intradermal versus scratch or prick tests are better—whether to use small intracutaneous therapy or massive subcutaneous therapy, whether to use preseasonal, coseasonal, or perennial therapy for pollenosis. We all have our own ideas on each of these matters, but what should be the accepted STANDARD? Do we yet know what we are doing when we give injection treatments? Certainly, the theory of the "blocking antibody" is a good working hypothesis—but is it the whole answer?

Even our terminology of basic scientific language is not universal. Confusing are the words of idiosyncrasy, hypersensitivity, sensitivity, intolerance, desensitization, hyposensitization, incubation period vs sensitization period, atopic vs nonspecific, anaphylaxis vs idiosyncrasies and *ad infinitum*.

Is it any wonder then, why our nonallergy friends in our profession look askance and mystified when we send our patients out-of-town with their own little bottles of extracts and special instructions; or when they

send some patient to two different allergists for opinions and get back two different types of reports of sensitivity reactions?

As you all recognize, there is an urgent need for the utmost cooperation among all interested in allergy. I feel that there should be a liaison joint committee to draw up certain standards, at least of a temporary nature, until more basic knowledge is accumulated. This joint committee should consist of members of the Academy, College, Foundation, and National Institutes of Health.

Other similar joint committees should be established to evaluate and study the educational fields, testing of new therapy, pollen and fungi surveys, and many other subjects. This would save all of us a lot of time, prevent an overlapping of work, and give us the united front in allergy which we so desperately need. For example, it has been most embarrassing at times, to hear a dean of a medical school say, "What, another survey on allergy education from another group. Why can't you fellows get together? Don't you trust each other?"

These are some of the basic problems we must solve. Perhaps with the help of new research made possible through the National Institute of Allergy and Infectious Diseases we will get some of these answers in the future. Won't it be wonderful when we say, for example, that Mrs. X. has bronchial asthma, Class 1-A, and is receiving 20,000 mg of substance Y every other week and that her respiratory function is Grade B, and everyone in the field would know exactly what it is and how to treat it.

During the past year the extramural budget of the National Institute of Allergy and Infectious Diseases was about 8¾ million dollars. Of this amount, well over $1,100,000 was allocated for seventy-three grants for research in allergy in universities, medical schools, schools of public health, hospitals, and other institutions. This was 9.6 per cent of the total number of grants, but 13 per cent of the total amount of money. This is considerably more money than had ever been spent previously for research in allergy. As you know, this same Institute deals with many other specialties including infectious diseases (tuberculosis), serology, parasitology and tropical medicine, virology, and immunology. Hence, allergy is certainly getting its fair share from this Institute. If we were to add an additional 3 million dollars approved for grants in immunology and the subjects related to allergy (in all forms), we would have over $4.5 million for research in allergy and immunology.

The individual grants in allergy varied from $1,150 to $64,000 and cover subjects of all types from enzyme chemistry to airborne allergens. Certainly, research in allergy has made a step forward, and much should come of all of this.

In addition to the extramural grants of this Institute, an intramural program was started on January 1, 1957. Dr. Jules Freund is Chief of the Laboratory of Immunology. At present there are twelve staff mem-

bers, but a sizable increase will be made next year. The present studies are with fundamental problems related to hypersensitivity. As the program develops, studies will be made in clinical allergy and other areas such as immunochemistry and nonspecific mechanisms.

Although this is all very wonderful news, I feel that medicine, our specialty included, should not completely be subsidized by and dependent on the National Government. Private sources of funds for research and investigation should still be sought for through various industries and foundations. There should be a close liaison between the public funds and private organizations. We are, indeed, fortunate that we have such a liaison unit in the American Foundation for Allergic Diseases.

Besides the activity of public education by the publishing and distribution of the excellent booklets on hay fever and asthma, and other lay literature, the Foundation has been active this year in several other activities:

(1) Surveying undergraduate and graduate training in allergy in our medical schools.

(2) Granting ten $500 stipends to medical students during the past summer for work in clinical allergy, and in the basic sciences related to allergy.

(3) Awarding two pre-doctoral fellowships of $2,500 and one $1,500 part-time fellowship.

The Foundation has many excellent plans for the future for public education, training of medical students and graduates in allergy, as well as fellowship training in allergy, patient care, and research.

Certainly, with all of these funds available and concentrated effort expended we should look for solutions to the many problems in our fields and not just the questions brought up earlier of standardization, et cetera. This makes the future in allergy very bright and our specialty very exciting at this time.

Techniques to study and treat such things as drug allergy, the wide spectrum of collagen diseases, nephritis and rheumatic fever will broaden our field of allergy rather than narrow it.

Many of you probably remember the questionnaire sent out in the International Correspondence of Allergy Letters a few years back. It asked, "Would you advise a young man getting out of medical school to go into allergy as a specialty?"

You recall, I am sure, the many types of responses to this question. But it appeared that the greatest number of those men answering would not recommend allergy as a specialty. They claimed that with the advent of antihistamines and then steroids, their practices were dwindling and there was no future in allergy. Nothing is further from the truth in my opinion! I feel that there are more opportunities for research and development in applied immunology and allergy, in the broad sense, than

in any other branch of medicine. There are so many old problems yet unanswered.

Some of these great therapeutic aids in allergy have been the antihistamines and steroids. However, we, as allergists, did not develop these agents, and we don't even know how they work! How much progress have we made in the following conditions: chronic atopic eczema, so-called intrinsic or infectious asthma, and chronic urticaria, over the past twenty to thirty years? At our medical meetings now, we are still discussing these same problems that confronted us two or three decades ago. Are we any nearer the solutions?

We need basic research in these fields, as we have been stymied with our clinical investigations. Allergy will need the help of physiologists, biochemists, enzyme chemists, and pharmacologists. We will have to become familiar with the newer techniques for investigations. We can no longer rely on a few test tubes and guinea pigs, pipettes and a water bath for research. We must learn of the intricacies of electrophoresis, ultracentrifuges and supracentrifuges, electron-microscopes, tissue cultures, virology, radioactive isotopes, enzymology, and immunochemistry. These required well-trained people with basic knowledge, and the carrying out of these tasks obviously necessitates large, well-equipped and expensive laboratories. It will be only with joint effort of all branches of the basic sciences that we can hope for solutions to many of our problems.

Exploring these many facets and establishing such setups for research are now possible through the National Institutes of Health and the American Foundation for Allergic Diseases. Allergy has much to look forward to in the future!

All of you must sense we are on the threshold of great things to come. Perhaps we will be able to treat our hay fever patients with radioactive pollen extracts with a half-life of thirty years or more and only one injection, or swallow of an "atomic pollen solution" will be the answer—it seems far-fetched, doesn't it—but so did guided missiles, rockets and interplanetary travel twenty years ago.

These are exciting times in allergy. We are indeed fortunate that there is such a cordial relationship between our two societies. However, the task ahead of us requires much closer, active cooperation, not just with medical economics or politics, such as certification and formation of a Section on Allergy, but, more important, the educational and scientific aspects of our specialty as I described earlier. This cooperation must extend beyond just our societies and should include the Foundation, the National Institutes of Health, and any other interested groups.

*Forty North Street*

# NASAL REACTIONS TO POLLEN AND ODOR OF ROSES

## Clinical Features, Mechanisms, and Prevention by Premedication

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THE ALLERGIST is confronted with other than purely allergic processes in the nasal cavity. Infection, hormonal deficiencies,[6] emotional reactions, nonspecific irritation and vasomotor instability may mimic or complicate allergy. The nasal mucous membrane may show the effects of any and all combinations of these processes, but among the commonest effects with which we have to contend are psychogenic ones which imitate and/or accompany allergic effects.

The nasal cavity should lend itself well to a proper assessment of these effects, for objective criteria such as membrane color, breathing space (inverse to the congestion of the membrane), and type, amount and content of nasal secretion, are directly observable. Surprisingly, reliable observations are extant only for the differentiation of allergy and infection.[4]

True allergy to the pollen of roses is not common and is rarely, if ever, the sole or primary cause of a patient's symptoms. Subjective reactions, however, to the odor of roses, both in allergic and nonallergic individuals, are common. They are so common, indeed, that seasonal allergic rhinitis or pollenosis was once known as "rose cold," almost as inaccurate a term as "hay fever." It appeared that a series of experiments exposing a group of patients to both the pollen and the perfume of roses might yield criteria for differentiating the effects of allergic and psychogenic mechanisms. If, in addition, this beloved insect-pollinated aristocrat of flowers could be exonerated from much unmerited blame, so much the better. The prophylactic effects of sympathomimetic drugs, antihistamines, and 11-oxysteroids on intranasal phenomena resulting from psychogenic stimulation have not been adequately described. Therefore, it appeared worth while to study also the effects of preliminary administration of epinephrine subcutaneously, tripelennamine orally, and hydrocortisone orally.

### SUBJECTS, MATERIALS AND METHODS

The thirty-eight subjects comprised twenty-two women and sixteen men ranging in age from seventeen to forty-six years. Included were six normal women and four normal men who had completely negative histories

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Pyribenzamine®, the Ciba brand of tripelennamine was used in these experiments.

of nasal or allergic difficulties and reacted negatively on skin-testing to grass and rose pollens. Twenty-eight subjects were patients that gave histories of sneezing, nasal blockage and nasal discharge occurring either seasonally or on exposure to roses. Six of the patients who claimed allergy to roses had negative skin tests to its pollen. The other twenty-two patients had positive skin tests to grass pollens or to grass pollens and rose pollen. None of the patients had any polyps or significant turbinate and/or septal abnormalities. None of them were victims of major emotional conflicts. None had received desensitization treatment. All were asymptomatic at the time the tests were made. The tests were performed between September and February in order to avoid the season of maximal grass pollenation. The room in which the tests were performed was maintained at 66 to 68 degrees Fahrenheit in order to eliminate effects due to temperature variation.

The rose pollen employed was collected from species cultivated with special precautions to prevent contamination with common airborne pollens, particularly of grasses. A 5 per cent extract in 50 per cent glycerosaline was used for scratch-testing, and a 1:20 dilution in phenol-saline for intradermal tests when the scratches were negative. For the insufflation tests, the pollen was blown directly into the nose.[3] At separate sessions each patient was insufflated with inactive pine pollen, rose pollen and a mixture of timothy, Bermuda and perennial rye grass pollens, with the object of establishing a standard of nasal reaction for positive and for negative skin reactors. There was no ascertainable insufflation reaction in any subject who had given a negative skin reaction to the pollen used.

A completely synthetic rose perfume, to the individual components of which no patient reacted subjectively* or objectively, was used in addition to the natural perfume. Whatever the noted reactions in any subject, they were identical to the two perfumes, whose odors were indistinguishable except by experts. Preliminary trials with comparable strengths of ethyl alcohol yielded no observable effects. Any pollen in the natural perfume must have been denatured during the perfume extraction process; certainly the synthetic perfume** could not have had any pollen in it.

Previous observations had revealed that any nonspecific effects from nonallergenic particulate matter in the nose disappeared within three minutes, and that allergic reactions could occasionally be delayed as much as one hour after intranasal insufflation. Therefore, intranasal observations

*Patients were told that these were simple synthetic chemicals, to which allergic reactions were impossible. This was a necessary but pardonable inaccuracy.

**Synthetic rose oil contained Citronellal 30.0 per cent, Rhodinol Alcohol 25.0 per cent, Phenylethyl Alcohol 18.5 per cent, Cinnamyl Cinnamate 6.0 per cent, Linalol 5.0 per cent, Alpha Ionone 4.0 per cent, Nonyl Alcohol 3.0 per cent, Benzyl Iso-Eugenol 3.0 per cent, Hydroxycitronellal 2.5 per cent, Benzyl Acetate 1.5 per cent, Phenylacetic Acid 1.0 per cent, Phenylethyl Formate 0.2 per cent, Aldehyde C9 0.1 per cent, Aldehyde C11 0.1 per cent, and Aldehyde C12 0.1 per cent (Total 100.0 per cent). Eight per cent is used in ethyl alcohol for perfume. (The usual 2 per cent of fixative necessary for persistence was not used in these experiments.)

were made just prior to testing and at intervals of five minutes, fifteen minutes and sixty minutes after testing. Mucous membrane swelling was graded 1 (slight diminution of breathing space), 2 (moderate diminution of breathing space) and 3 (complete blockage). Pitting edema was ascertained by pressure with a blunt probe on the inferior turbinate. Sneezing was recorded as O (absent), I (isolated) or P (paroxysmal). Secretions, when elicited, were collected on applicators or cellophane handkerchiefs. Smears were stained by Hansel's method and eosinophilia was graded N (normal), 1, 2, 3 and 4 according to his standards.[4]

Drugs were tested separately for their prophylactic effects with the following dosage and timing before the pollen and perfume trials:

Tripelennamine—15 mg per 30 pounds body weight orally thirty minutes before.

Epinephrine—0.1 cc of 1:1,000 per thirty pounds body weight subcutaneously twenty minutes before.

Hydrocortisone—A dose of 1 mg per pound of body weight was approximated. One-third of this was taken orally at bedtime the night before, one-third on arising, and one-third in the afternoon approximately one hour before the trial.

## RESULTS

To facilitate recording and analysis of results, the subjects were divided as follows into six groups on the basis of history of nasal symptoms in the presence of roses, and skin tests with grass pollens and rose pollen:

Group A. Negative history; skin test negative to grass pollens and rose pollen; normal controls.

Group B. Positive history; skin test negative to grass pollens and rose pollen.

Group C. Negative history; skin test positive to grass pollens and negative to rose pollen.

Group D. Positive history; skin test positive to grass pollens and negative to rose pollen.

Group E. Negative history; skin tests positive to grass pollens and to rose pollen; not told of their positive skin reactions to rose pollen.

Group F. Negative history; skin tests positive to grass pollens and rose pollen; told of their positive skin reaction to rose pollen.

Groups C, D, E and F were composed of the twenty-two patients who were sensitive to grass pollens on skin testing. The following reactions were obtained in them by intranasal insufflation of grass pollen mixture: Sneezing began within three minutes, sometimes within seconds, and it came in paroxysms. The sneezing never subsided in less than fifteen minutes and was still present in a few instances at the end of an hour. At the end of the five-minute period, the mucous membrane was markedly redder than normal in all the cases. At the fifteen-minute observation the membranes of fourteen patients (64 per cent) were still hyperemic, and at sixty minutes the membranes of all the patients were moist and grayish or bluish-white. Swelling of the membrane started promptly, attaining either grades 2 or 3 at the five-minute observation, and grade 3 (complete blockage) in every case at the fifteen-minute observation. The

TABLE I. EFFECTS OF INHALATION OF ROSE PERFUME ON NOSES OF PATIENTS IN GROUP B.

| Age and Sex | Sneezing | Swelling of Mucous Membrane | Color of Mucous Membran | Discharge | Eosinophils | Prevention of Reaction by | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Tripelennamine | Epinephrine | Hydrocortisone |
| 28 M | 0 | 0 | U | 0 | x | x | x | x |
| 33 M | 0 | 0 | U | 0 | x | x | x | x |
| 41 F | 0 | Grade 1 | U | Slight Mucoid | N | No | Yes | No |
| 18 F | I | Grade 1 | U | 0 | x | No | Yes | No |
| 32 F | 0 | Grade 1 | R | 0 | x | No | Yes | No |
| 26 F | I | Grade 2 | R | Slight Mucoid | N | No | Yes | Yes |

I—isolated. U—unchanged. R—reddened. N—normal proportion. x—not performed.
Note: All membranes were back to normal by the end of the sixty-minute observation period.

one-hour observation still revealed moderate or complete blockage in most cases, and pitting could be elicited by gentle pressure on the inferior turbinate with a blunt probe. Discharge was variable in consistency and amount, but was always obtainable by applicator or blowing into cellophane sheets; in fifteen patients (68 per cent) it was watery and in seven (32 per cent) it was mucoid. Eosinophilia ranging from grades 2 to 4 by Hansel's criteria was present at either the fifteen-minute or sixty-minute inspection, depending upon when secretion was obtainable; the sediments of the watery ones were concentrated by centrifuging. A few patients had lacrimation and conjunctival injection and two experienced mild asthma. The nasal reactions were terminated by saline washing and 0.25 per cent phenylephrine spraying. Epinephrine subcutaneously terminated the asthma.

Nine of the twenty-two grass-pollen-sensitive patients who were also sensitive to rose pollen on skin testing underwent similar insufflation of rose pollen at separate sessions. The observed phenomena were qualitatively the same as with grass pollens but a little slower in developing and not quite as intense. The other thirteen patients had no ascertainable reaction to rose pollen insufflation after the initial brief nonspecific irritation.

### EFFECTS OF ROSE PERFUME INHALATION AND OF PROPHYLACTIC TREATMENT

*Group A.*—(Six women, aged twenty-one, twenty-four, thirty-three, thirty-four and forty-six, [one, age not given]; and four men, aged nineteen, twenty-six, thirty-six, and forty-three.) This group had no subjective or objective reactions to the intranasal insufflation of grass or rose pollens, or to the inhalation of natural or synthetic rose perfume. It was not necessary, therefore, to conduct any prophylactic epinephrine, tripelennamine or hydrocortisone tests in this group.

*Group B.*—This group had no reaction to intranasal insufflation with rose pollen. When they were allowed to inhale rose perfume, the effects shown in Table I were obtained within fifteen minutes.

No change occurred in the two male patients. Of the four female pa-

TABLE II. EFFECTS OF INHALATION OF ROSE PERFUME ON NOSES OF PATIENTS IN GROUP D.

| Age and Sex | Sneezing | Swelling of Mucous Membrane | Color of Mucous Membrane | Discharge | Eosinophils | Prevention of Reaction by | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Tripelennamine | Epinephrine | Hydrocortisone |
| 21 F | 0 | 0 | Slightly reddened | Slight Mucoid | N | No | Yes | No |
| 17 F | 0 | 0 | U | 0 | x | x | x | x |
| 26 F | I | Grade 2 | Slightly reddened | Slight Mucoid | N | No | Yes | No |
| 44 M | 0 | 0 | U | 0 | x | x | x | x |
| 30 F | 0 | Grade 1 | R | 0 | x | No | Yes | No |

I—isolated. U—unchanged. R—reddened. N—normal proportion. x—not performed.
Note: All membranes were back to normal by the end of the sixty-minute observation period.

tients, there was some swelling of the membrane in all, occasional sneezing in two, and reddening of the membranes in two. Epinephrine prevented a reaction in all four females, hydrocortisone in one of them and tripelennamine in none.

*Group C.*—(Three women, aged twenty-three, twenty-nine and thirty-seven; five men, aged twenty-two, twenty-five, thirty, thirty-two and forty-four). There were absolutely no subjective or objective effects from the inhalation of rose perfume; it was unnecessary, therefore, to repeat such tests with preliminary medication. All of these eight patients reacted positively to intranasal grass pollen insufflation as described previously, and these tests were repeated with preliminary medication with the following results: Epinephrine completely prevented mucous membrane color changes, swelling, discharge (and eosinophilia), as well as sneezing. Tripelennamine was a good suppressant, holding the changes, when present at all, to minor grades. Hydrocortisone was a somewhat better inhibitor, midway in efficacy to tripelennamine and epinephrine.

*Group D.*—All in this group had reacted to intranasal insufflation with grass pollens but not rose pollen. When they were allowed to inhale rose perfume, the effects shown in Table II were obtained within fifteen minutes.

No change occurred in the male patient. Of the four female patients, there was sneezing, swelling, and slight reddening of the mucous membrane with slight mucoid discharge in one patient, swelling and reddening of the mucous membrane in another, and reddening of the mucous membrane and mucoid discharge in a third; one showed no change. Epinephrine prevented the reaction in all three reactors but tripelennamine and hydrocortisone did not.

*Group E.*—(Two women aged twenty-seven and thirty-six; three men, aged twenty-two, thirty and thirty-nine). When the patients in this group were allowed to inhale rose perfume, there were no subjective or objective effects. The prophylactic drug tests were therefore not performed.

TABLE III. EFFECTS OF INHALATION OF ROSE PERFUME ON NOSES OF PATIENTS IN GROUP F.

| Age and Sex | Sneezing | Swelling of Mucous Membrane | Color of Mucous Membrane | Discharge | Eosinophils | Prevention of Reaction by | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Tripelennamine | Epinephrine | Hydrocortisone |
| 39 F | I | Grade 1 | R | Slight Mucoid | N | No | Yes | No |
| 35 M | 0 | Grade 1 | Slightly reddened | 0 | x | No | Yes | No |
| 43 F | I | Grade 2 | Slightly reddened | Slight Mucoid | N | No | Yes | No |
| 19 F | 0 | 0 | U | 0 | x | x | x | x |

I—isolated. U—unchanged. R—reddened. N—normal proportion. x—not performed.
Note: All membranes were back to normal by the end of the sixty-minute observation period.

*Group F.*—When the patients in this group were allowed to inhale rose perfume, the effects shown in Table III were obtained within fifteen minutes.

In the male patient there was swelling and slight reddening of the mucous membrane. In two of the three female patients there was sneezing, swelling and reddening of the mucous membrane with slight mucoid discharge. The third female patient did not react. Epinephrine prevented the reaction in all three reactors, but tripelennamine and hydrocortisone did not.

Pitting on pressure was never obtainable in any of the membranes that were swollen after perfume inhalation and no gray or bluish-white color was ever observed. It is of interest that subsequently, on separate occasions in six of the ten perfume "reactors" in Groups B, D and F, a few isolated sneezes and slight nasal blockage were elicited by bringing odorless artificial roses into the examining room.

## SUMMARY OF RESULTS

In the patients studied, when the skin tests were negative the intranasal pollen tests were negative. When the skin tests were positive the intranasal insufflation of the corresponding pollen caused the typical signs and symptoms of "hay fever"—paroxysms of sneezing, nasal blockage and watery discharge with increased eosinophils, and initial redness with later grayness and pitting edema of the nasal membrane. The reactions to intranasal pollen insufflation could be completely prevented by epinephrine and almost completely prevented by hydrocortisone and tripelennamine, the former being slightly more efficient.

Inhalation of rose perfume usually produced no change in the color of the mucous membrane. In some cases it was reddened, usually slightly, but it never became gray or bluish-white. Swelling was never above moderate (Grade 2), if present at all, and pitting could never be elicited. Discharge was present in only six of the fifteen cases in Groups B, D and F, and was small in amount, and mucoid; eosinophils were absent or present only in normal proportion. The discharge never became watery, and

sneezing was never paroxysmal or continuous. All reactions obtained were at their height or beginning to subside at the fifteen-minute inspection, and all patients were subjectively and objectively normal at the sixty-minute observation.

Pollen reactivity and perfume reactivity were completely independent and were qualitatively and quantitatively different. Nasal reactivity to pollen in the subjects studied always accompanied positive skin tests. Reaction to rose perfume seemed to be determined by the patient's preconceived ideas, or by a knowledge of a positive skin test to rose pollen. Ten patients, nine female and one male, showed objective changes to perfume inhalation. These could be prevented in all ten by epinephrine, in only one by hydrocortisone, and in none by tripelennamine. It is conceivable that the subjects who reacted nasally to the natural and synthetic perfumes could be truly allergic to the natural perfume. It is highly unlikely, however, for they did not react to the individual components of the synthetic perfume, and these are presumably the same or main ingredients of the natural perfume. The ratio of nine women to one man among the perfume reactors would seem to indicate that women are more amenable to suggestion and/or conditioning, where odors are concerned.

## DISCUSSION

True allergic reaction in the nasal mucous membrane is visualized as an antigen-antibody reaction, wherein the antigen is absorbed directly at the site or is transported there from another location by the lymph-vascular system. An important, if not sole, result of this antigen-antibody union on sensitized cells is a release of histamine or histamine-like substance, with consequent capillary dilatation, increased capillary permeability and stimulation of secretion.[5] This tissue reaction or its consequences can be counteracted by three mechanisms: (1) The 11-oxysteroids do not affect the antigen-antibody union and in therapeutic doses do not diminish antibody production, but they could protect the cells from damage and thus prevent histamine release.[7] These compounds are also involved with the inactivation of released histamine. (2) Since epinephrine is a direct pharmacologic antagonist to histamine it should be effective prophylactically. (3) An antihistaminic blocking agent could be effective by occupying the reactive sites on the cells so that histamine could not react even if released. In these experiments a clinical test was made of each possibility.

In the case of psychogenic reactions or nasal neuroses, the cerebral or thalamic stimulation received through the fifth cranial nerve afferents sets off a chain of impulses in which the medulla, spinal cord and autonomic nervous system are successively involved, the final effectors being the autonomic fibers to the vascular supply of the nasal mucous membrane. The ineffectiveness of an antihistamine in preventing this reaction is in accord with the lack of evidence involving histamine in psychogenic reactions. The lack of protection from 11-oxysteroid administration is in

accord with our knowledge that cell damage is not involved. The effectiveness of epinephrine is evidence for the involvement of a vasomotor mechanism, for the only action that epinephrine could have under these circumstances is vasoconstriction; there was not enough time under the conditions of the experiments to stimulate the hypothalamic-anterior pituitary-adrenal cortex mechanism.

Psychosomatically speaking, the nose may respond in two ways, each employing a different neural pathway. The response to fear, sadness or other emotions involving little or no conflict is one of nasal hypofunction (pallor, dryness and thinness of the mucous membrane). It results from predominance of sympathetic activity by way of adrenergic fibers from the cervical sympathetic ganglia.[1] This is an offensive type of reaction and was not observed in these experiments.

The response evoked by noxious stimuli and by emotions such as resentment, frustration, humiliation, anxiety, et cetera, producing conflict, and involving either real or implied threat to the organism, is one of nasal hyperfunction.[8] The initial stage is characterized by hyperemia, swelling of the mucous membrane with blockage, and lowering of the pain threshhold. The final stage, after prolonged hyperemia, turgescence and hypersecretion, involves pallor and edema. Only the initial stage in mild or moderate degree was observed in these perfume experiments. This defensive and protective type of reaction, which "shuts out" and "washes away" either literal or symbolic threats, results from preponderance of parasympathetic activity via cholinergic fibers carried by the greater superficial petrosal nerve.[2,8] The afferent fibers are provided by the fifth cranial nerve, some of its fibers traveling with the greater superficial petrosal nerve. Eyes, bronchioles, diaphragm and even the esophagus may participate in this "shutting out" process, which results in a diminution of exchange with the patient's environment.

In the perfume-reacting subjects, the pleasant odor could not be considered as literal noxious threat, but it was considered a symbolic one. A person not infrequently smells roses at the same time he is breathing a pollen or other inhalant to which he is genuinely allergic, and the odor may become unpleasantly associated with the subsequent allergic episode. Then, too, it is only human nature to try to associate one's troubles with something that can be actually touched, smelled or seen without the aid of a microscope. To the pure physiologist, the response to perfume could be considered a conditioned reflex of the Pavlov type in the reactors in Groups B and D, but not in the reactors in Group F; here there was no time for the classic conditioning by association.

A "contact rhinitis" from the volatile oils analogous to contact dermatitis is a theoretic possibility. A slower onset and longer duration of the observed changes would be expected, however. Also expected would be inhibition by hydrocortisone and lack of inhibition by epinephrine, effects opposite to those actually observed.

## SUMMARY AND CONCLUSIONS

1. In subjects that were skin-test positive to grass pollens and to rose pollen, a typical hay fever reaction, including pitting edema of the membrane and profuse secretion with abnormally high eosinophil content, could be elicited by intranasal insufflation with the pollen. The insufflation reaction could be prevented completely by premedication with epinephrine subcutaneously. Oral hydrocortisone and tripelennamine premedication allowed only borderline changes, if any.

2. In seven of eleven subjects who believed they were allergic to roses but who were skin-test negative to rose pollen, and in three out of four subjects who previously claimed they were not allergic to roses but who had been told of recent positive skin reactions to rose pollen, the inhalation of rose perfume produced isolated sneezes and transient mild or moderate hyperemia, never progressing to edema. The nasal secretion, when obtainable, was mucoid and never profuse or abnormal in eosinophil content. The reaction could be prevented by epinephrine, but not by tripelennamine or hydrocortisone (with one exception), indicating that the reaction was probably neurovascular.

3. When the subjects were allowed to inhale rose perfume, the reaction obtained in a subject was the same whether the natural or the synthetic product was used. No subject reacted to inhalation of the individual ingredients of the synthetic perfume.

4. The odor of roses is often perceived just before or during the time a patient is having symptoms from diverse causes, including the inhalation of particulate matter to which he is truly allergic. The odor then becomes a symbolic threat to the integrity of the organism by association, and the autonomic nervous system reacts by parasympathetic preponderance. The intent of this defensive reaction is to shut out and wash away the threatening agent. In the majority of such cases the reaction could be regarded as a conditioned reflex of the Pavlov type.

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# AIRBORNE MOLD FLORA OF THE ATLANTA AREA, 1953-1954

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AGAR plate counts of airborne molds were undertaken in February, 1953, at three sites in and near Atlanta, Georgia. Results for the period February, 1953, to April, 1954, are reported here as a contribution to the study of inhalant allergenic fungi.

The view, first advanced by Prince, Selle and Morrow[8] and by Feinberg,[3] that mold spores are common causes of inhalant allergy in the United States, has been definitely established. Recently, the clinical importance of airborne mold counts was emphasized by the report of Schaffer, Seidmon and Bruskin,[9] who found a definite correlation between colony count and positive skin tests. They concluded that, with few exceptions, the most commonly found organisms give the greatest number of clinical reactions.

In his 1942 review of fungus spore distribution in the air over various localities, Durham[2] listed gravity slide counts of *Alternaria, Hormodendrum,* and rust spores obtained in Atlanta in 1933 and 1937. However, no reference to published reports of plate counts in this vicinity has been found. Griffith[5] conducted studies in the Savannah area in 1950, and more recently Collier and Ferguson[1] performed plate count surveys over a period of a year (1952) at Brunswick, Georgia.

In the present study particular search was made for the presence of infectious pathogenic fungi in the air. The only finding referable to this category was a lone isolate of *Aspergillus fumigatus.*

## PROCEDURE

Sampling was begun in February, 1953, and carried on through April, 1954.* The three sites chosen for comparison were: a) a waist-high, west-facing outdoor window ledge at Chamblee, an Atlanta suburb, in an area of grassy vegetation obstructed to some extent by small buildings; b) a shrubbed terrace, eighteen inches high, outside the south entrance to a downtown Atlanta office building; and c) either a desk or the floor inside the well-traveled, glass-enclosed lobby of the same building. Sampling was performed on each of twenty-eight dates, and a total of 829 colonies, comprising forty-nine genera and a few sterile mycelia, were isolated and

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*It was intended originally to make collections weekly at each of three sampling sites, but press of other work forced elimination of many of the scheduled dates, so that the intervals employed were irregular, although in weekly multiples, extending finally to monthly periods. All three sites were utilized each time except for the last four dates, on which collections were restricted to a single station.

identified. Meteorologic data for each of the sampling dates (except the first three), representing conditions at Chamblee at the actual time of exposure, were obtained from the Aerology Office, U. S. Naval Air Station, Chamblee.

All sampling was accomplished by simultaneous exposure for twenty minutes at each of the three sites, at approximately 1:00 p.m. on each sampling day, of a 100 mm Petri dish containing either Czapek-Dox or potato dextrose agar (PDA). The latter medium was employed exclusively at first, but was soon replaced. On the last four dates, plates of both Czapek-Dox and PDA were exposed in parallel for direct comparison of the media. Following exposure all plates were incubated at room temperature, exposed to natural diurnal light variation, and examined at frequent intervals for at least two weeks, beginning on the third or fourth day of incubation. Initially all colonies were transferred to slants of the two above media for later identification, unless readily recognized macroscopically on the exposure plate. Subsequently, it was found more efficient to identify the colonies directly upon the transparent Czapek plates under low magnification (100X) of the compound microscope, occasional employment of high power (440X) being necessary to confirm identification. Those colonies not sporulating upon the Czapek plates were transferred to slants of the same medium, and of PDA, for further study. If ultimate sporulation failed on these media the mold was counted as either "sterile hyaline" or "sterile dark." The rare yeasts appearing on the exposure plates were disregarded.

## RESULTS

Of 829 mold colonies which appeared on the plates, 808 were assigned to a total of forty-nine genera, twenty-one isolates remaining unidentified owing to failure to sporulate. Table I shows distribution of the predominant genera according to date of collection and sampling site. In addition, the following organisms were identified (the figures indicate respective totals for the entire sampling period): *Acrotheca* one, *Botryosporium* one, *Cephalosporium* ten, *Chaetophoma* one, *Chalara* one, *Coniothecium* one, *Cryptomela* one, *Dothiorella* three, *Fusidium* eight, *Geotrichum* two, *Gliobotrys* one, *Hormiscium* one, *Monilia* one, *Monotospora* one, *Mucor* four, *Nigrospora* three, *Paecilomyces* eight, *Pestalozzia* five, *Physospora* eight, *Pseudoplea* four, *Pyrenochaeta* two, *Rabenhorstia* one, *Rhizoctonia* four, *Rhizopus* five, *Scopulariopsis* four, *Spicaria* two, *Sporobolomyces* two, *Syncephalastrum* two, *Thielavia* two, *Tricellula* two, *Trichoderma* two, *Trichosporium* one, *Verticillium* one, and *Zythia* one.

The twenty-three colonies of *Aspergillus* were separated further as follows: *A. niger* twelve, *A. flavus* four, *A. versicolor* three, *A. fumigatus* one, *A. terreus* one, unidentified species two. Species identification was not otherwise attempted except for *Monilia* (*M. sitophila* one), *Pseudoplea gaumanni* and *Tricellula inaequalis*. One of the four isolates of *P.*

**TABLE I. IDENTITY AND COUNT OF PRINCIPAL AIRBORNE MOLDS 1953-1954**

| Date* | 2-16 | | | 2-22 | | | 3-3 | | | 3-23 | | | 3-30 | | | 4-6 | | | 4-13 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Site | A | B | C | A | B | C | A | B | C | A | B | C | A | B | C | A | B | C | A | B | C |
| 1. *Alternaria* | 4 | | | | 3 | | | | | | | | 1 | 2 | 1 | | 5 | | 2 | 3 | |
| 2. *Aspergillus* | | | | | | | | | | 1 | 1 | 2 | | | | | | | | | |
| 3. *Coniothyrium* | | | | | | | | | | | | | | | | | 13 | | 1 | | |
| 4. *Curoularia* | | | | | | | | | | | | | | 1 | | | | | 1 | | |
| 5. *Epicoccum* | 5 | 4 | | | | | | | 3 | | 2 | 3 | 1 | | | 1 | 3 | | 2 | | |
| 6. *Fusarium* | | | | | | | | | | | | | | | | | | | 2 | 1 | |
| 7. *Helminthosporium* | | | | | 2 | | | 5 | | | | 2 | | | | | | | | | |
| 8. *Hormodendrum* | 2 | 1 | 1 | | | | | | | | | | 2 | | | | | | | | |
| 9. *Oospora* | | | | | | | | | 1 | | | | | | | | | | | | |
| 10. *Penicillium* | | | | | | | | | | | | | 1 | 1 | | | | | | 2 | |
| 11. *Phoma* | | | | | | | | | | | | | | | | | 1 | 1 | 1 | 2 | 1 |
| 12. *Pullularia* | | | | 1 | | | | | 2 | 1 | | 2 | | | | 1 | | | | | |
| 13. *Sphaeronema* | | | | | 2 | | | | | | | | | 1 | | | | | | 1 | |
| 14. *Stemphylium* | | | | | | | | | | | | | | | | | | | | | |
| 15. *Streptomyces* | | | | | | | | | | | | | 2 | | 1 | 2 | 5 | 1 | 4 | 2 | |
| Total | 11 | 5 | 1 | 1 | 7 | 0 | 0 | 5 | 6 | 2 | 3 | 9 | 7 | 5 | 2 | 4 | 27 | 2 | 13 | 11 | 1 |
| Total, principal molds | 17 | | | 8 | | | 11 | | | 14 | | | 14 | | | 33 | | | 25 | | |
| Total, all molds | 17 | | | 12 | | | 19 | | | 18 | | | 16 | | | 40 | | | 28 | | |

| | 4-20 | | | 5-5 | | | 5-11 | | | 5-18 | | | 5-25 | | | 6-18 | | | 6-30 | | | 7-22 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | C | A | B | C | A | B | C | A | B | C | A | B | C | A | B | C | A | B | C | A | B | C |
| 1. | 1 | 1 | | 1 | 2 | 1 | 1 | | 1 | | | | | | | 1 | | 1 | | | 1 | | | 4 |
| 2. | | | | 1 | | 1 | | | | | 1 | 1 | | | | | | | | 1 | | | | 1 |
| 3. | | | 1 | | | | | | | | | | | | | | | | | | | | | |
| 4. | | | | 1 | | | | | 1 | 1 | | 1 | | | | 1 | | 1 | 1 | | | | 1 | |
| 5. | 2 | | | | | | | | | | | | | | | | | | | | | | | |
| 6. | | | | | | | | | | | | | | | | | 1 | | | | | | | |
| 7. | | | | | | | | 1 | | | | | | | | | | | 1 | | | | | |
| 8. | 1 | 1 | | | | | | | | | | | 3 | | | | | | | 1 | | | | |
| 9. | | | | | | | | | | | | | | | 1 | | | | | | | | | |
| 10. | 4 | | | | 1 | | | | | | | | | | 1 | | | | | | | | | |
| 11. | 1 | 2 | | | | | | | | | | | | | | | | | 1 | | | | | |
| 12. | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| 13. | | | | | | | | | | | | | | | | | | | 1 | | | | | |
| 14. | | | | | | | | | | | | | | | | | 1 | | | | | 1 | | |
| 15. | 2 | 1 | 2 | | | | | | | | | | 1 | | | 1 | | | | | 1 | 5 | 20 | 1 |
| | 11 | 5 | 3 | 3 | 3 | 2 | 1 | 1 | 2 | 1 | 1 | 2 | 4 | 0 | 2 | 3 | 2 | 2 | 4 | 2 | 2 | 6 | 22 | 6 |
| | 19 | | | 8 | | | 4 | | | 4 | | | 6 | | | 7 | | | 8 | | | 34 | | |
| | 24 | | | 9 | | | 8 | | | 5 | | | 6 | | | 8 | | | 9 | | | 41 | | |

*Potato dextrose agar used 2-16 to 3-30; Czapek's thereafter. Samples on 1-13 to 4-15, 1954 were taken only at site A.

*gaumanni,* all of which appeared identical, was identified to genus and species through the courtesy of Professor Frederick A. Wolf, Duke University. *T. inaequalis,* one colony of which appeared at each of sites A and B on different days, was regarded as an unidentified mold when first isolated on October 28. Subsequently there came to our attention an article by Dr. Agathe L. van Beverwijk[11] describing a similar organism obtained from the air in Norway. Dr. van Beverwijk has examined one of our cultures and has confirmed its identity with her *T. inaequalis.* We have described this mold elsewhere.[4]

The order of frequency of occurrence, i.e., number of days (of a total of twenty-eight) on which one or more colonies of each of the dominants appeared, is as follows: *Alternaria* twenty-two, *Streptomyces* nineteen,

TABLE I. (CONTINUED)

| | 8-5 | | | 8-19 | | | 9-2 | | | 9-15 | | | 10-1 | | | 10-14 | | | 10-28 | | | 12-4 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | C | A | B | C | A | B | C | A | B | C | A | B | C | A | B | C | A | B | C | A | B | C |
| 1. | | | | 2 | 8 | | 5 | 12 | | 3 | 1 | | 4 | 2 | | 8 | 4 | | 5 | 5 | | 1 | 1 | |
| 2. | | | | | | | | 1 | | 1 | 2 | 5 | | | | | | | | | | | 2 | |
| 3. | | | | | | | | | | | | | | | | | | | | | | | | |
| 4. | | 6 | 2 | 2 | | 3 | 1 | 1 | 5 | | 1 | | 1 | 6 | | | | | | | | | | |
| 5. | | | | | | | | | | 3 | | | | | | 1 | 1 | | 1 | | | 1 | | |
| 6. | | | | 2 | | | 2 | 1 | | 2 | | | | | | | 2 | | | | | | 1 | 1 |
| 7. | | | 2 | | 1 | | 10 | 3 | 2 | 3 | | | 1 | | | 1 | 3 | | 1 | | | 1 | | |
| 8. | | | | | 1 | | | 5 | 6 | 2 | | | | | | 22 | 6 | 1 | 17 | 5 | 5 | 2 | | 3 |
| 9. | | | | | 1 | | | | | | | | | | | | 1 | | | 1 | | 10 | 2 | |
| 10. | | | 2 | | | | 1 | 5 | 2 | 2 | | | | | | | | 1 | | | | 2 | | 1 |
| 11. | | | | | | | 1 | 4 | | 1 | | | | | | 1 | 1 | | | 1 | 2 | 2 | | |
| 12. | | | | | | | | | | 12 | | | | | | 1 | 1 | 1 | 4 | | | | 2 | |
| 13. | | | | | | | 1 | | | 1 | 1 | | | | | | | | 3 | | | | | |
| 14. | | 1 | | 2 | | | | 1 | 2 | 1 | | | | | | 4 | | 1 | | 2 | | | | |
| 15. | | 4 | 2 | 7 | 1 | | 8 | 23 | | | | | 1 | 2 | 2 | 7 | | 3 | | 3 | | | 4 | 3 |
| | 0 | 10 | 9 | 15 | 12 | 3 | 29 | 56 | 17 | 31 | 5 | 5 | 7 | 10 | 2 | 45 | 19 | 7 | 31 | 15 | 9 | 19 | 12 | 8 |
| | | 19 | | | 30 | | | 102 | | | 41 | | | 19 | | | 71 | | | 55 | | | 39 | |
| | | 20 | | | 33 | | | 119 | | | 49 | | | 21 | | | 78 | | | 63 | | | 50 | |

| | 12-15 | | | 1-3 | 2-17 | 3-17 | 4-15 | Total | | | Total | Frequency† | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | C | A | A | A | A | A | B | C | | A | B | C | Total |
| 1. | 7 | 1 | | 1 | 1 | | 5 | 53 | 50 | 9 | 112 | 18 | 14 | 6 | 22 |
| 2. | | 1 | | | | | 1 | 4 | 9 | 10 | 23 | 4 | 7 | 5 | 10 |
| 3. | | | | | | | | 1 | 13 | 1 | 15 | 1 | 1 | 1 | 3 |
| 4. | | 2 | 1 | | | | | 9 | 18 | 14 | 41 | 8 | 7 | 7 | 14 |
| 5. | 10 | 1 | | | | 2 | | 29 | 11 | 6 | 46 | 10 | 5 | 2 | 13 |
| 6. | | | 1 | | | | | 8 | 6 | 2 | 16 | 4 | 5 | 2 | 8 |
| 7. | 1 | | | 3 | | | 1 | 23 | 15 | 6 | 44 | 10 | 6 | 3 | 16 |
| 8. | 8 | 2 | | 2 | 2 | 2 | 22 | 87 | 22 | 16 | 125 | 13 | 8 | 5 | 16 |
| 9. | | | | | | | | 10 | 5 | 2 | 17 | 1 | 4 | 2 | 6 |
| 10. | | 1 | | | | | 3 | 13 | 10 | 7 | 30 | 6 | 5 | 5 | 12 |
| 11. | 1 | | | | | | 1 | 10 | 11 | 4 | 25 | 9 | 6 | 3 | 11 |
| 12. | 7 | | 7 | 1 | | | 5 | 33 | 4 | 12 | 49 | 9 | 3 | 4 | 12 |
| 13. | 1 | | | 1 | | | | 8 | 5 | | 13 | 6 | 4 | | 9 |
| 14. | | | 1 | | | | | 8 | 2 | 7 | 17 | 4 | 2 | 5 | 9 |
| 15. | 9 | | 2 | 1 | 3 | 3 | | 56 | 65 | 18 | 139 | 15 | 10 | 8 | 19 |
| | 44 | 8 | 12 | | | | | 352 | 246 | 114 | 712 | | | | |
| | | 64 | | 9 | 6 | 7 | 38 | | 712 | | | | | | |
| | | 72 | | 9 | 10 | 7 | 38 | 399 | 288 | 142 | 829 | | | | |

†Number of days of occurrence at each site. Total denotes number of days at any site.

*Hormodendrum* sixteen, *Helminthosporium* sixteen, *Curvularia* fourteen, *Epicoccum* thirteen, *Penicillium* twelve, *Pullularia* twelve, *Phoma* eleven, *Aspergillus* ten. The top ten molds, by total count were: *Streptomyces* 139, *Hormodendrum* 125, *Alternaria* 112, *Pullularia* forty-nine, *Epicoccum* forty-six, *Helminthosporium* forty-four, *Curvularia* forty-one, *Penicillium* thirty, *Phoma* twenty-five, *Aspergillus* twenty-three. The first three of this list comprised 45 per cent of the total count; all ten made up 76 per cent of the total.

The same top three were highest with respect to the frequency of dominance on any given day (Table II). Here, when two or more molds were present in equally high number both are listed as dominants. An organism represented only by a single colony was counted as dominant

**TABLE II. DOMINANT MOLDS, EACH DATE, EACH SITE**
(Figures in Parentheses Indicate Secondary Dominance)

| Site | *Streptomyces* | *Hormodendrum* | *Alternaria* | *Curvularia* | *Epicoccum* | *Pullularia* | *Aspergillus* | *Helminthosporium* | *Penicillium* |
|---|---|---|---|---|---|---|---|---|---|
| A | 3-30<br>4- 6<br>4-13<br>7-22<br>8-19<br>(9- 2)<br>(12-15)<br>2-17<br>3-17 | 3-30<br>5-25<br>10-14<br>10-28<br>(12-15)<br>(1-13)<br>(2-17)<br>(3-17)<br>4-15 | (2-16)<br>10- 1<br>(12-15) | | 2-16<br>12-15<br>(3-17) | 2-22<br>9-15<br>(12-15) | | 9- 2 | 4-20 |
| B | (4-13)<br>7-22<br>(8- 5)<br>9-12<br>12-14 | 10-14<br>10-28<br>12-15 | 2-22<br>3-30<br>4-13<br>5- 5<br>8-19<br>(9- 2)<br>(10-14)<br>10-28 | 8- 5<br>10- 1<br>12-15 | 2-16<br>(3-23) | | 5-18<br>9-15 | (2-22)<br>(3- 3) | (4-13) |
| C | 4-20<br>8- 5<br>10- 1<br>10-14<br>12- 4 | 2-16<br>9- 2<br>10-28<br>12- 4 | 7-22 | 8- 5<br>8-19<br>(9- 2) | 3- 3<br>3-23 | (3- 3)<br>(3-23)<br>12-15 | (3-23)<br>9-15 | (3-23)<br>8- 5 | 8- 5 |
| Tot. (ABC) | (3-30)<br>(4- 6)<br>4-13<br>4-20<br>7-22<br>(8- 5)<br>(8-19)<br>9- 2<br>(12-15) | 5-25<br>10-14<br>10-28 | 2-22<br>3-30<br>(4-13)<br>5- 5<br>5-11<br>6-18<br>8-19<br>(9- 2)<br>(10- 1) | 5-18<br>6-18<br>8- 5<br>10- 1 | 2-16<br>3-23<br>(12-15) | 9-15<br>12-15 | (3-23)<br>5-18<br>(9-15) | (2-22) | (4-20) |
| Days Dom. | 19 (9) | 15 (4) | 14 (7) | 9 (1) | 7 (3) | 5 (3) | 4 (3) | 2 (4) | 2 (2) |

Also: *Phoma* (4-13), 4-20B, 4-13C; *Physospora* 3-3A, B & Tot.; *Coniothyrium* 4-6B & Tot.; *Oospora* 12-4A & Tot.; *Pestalozzia* 2-22C & Tot.; *Rhizopus* 3-23B, (3-23) Tot.; *Sphaeronema* (2-22) B & Tot.; *Mucor* 4-20B.

when no other species appeared. The figures in parentheses represent "secondary dominants," that is, those organisms having a lower count than the dominant but still considerably higher than the rest. The order of frequency of dominance, totaling the individual sites together with the over-all daily count, as shown in Table II, was: *Streptomyces* nineteen (nine), *Hormodendrum* fifteen (four), *Alternaria* fourteen (seven), *Curvularia* nine (one), *Epicoccum* seven (three), *Pullularia* five (three), *Aspergillus* four (three), *Helminthosporium* two (four), *Penicillium* two (two), *Phoma* two (one).

The graph in Figure 1 depicts seasonal variation of principal meteorologic factors in comparison with total mold counts for the respective dates. Counts of each of the most important organisms underwent a distinct seasonal change, which appeared to have some relationship to both temperature and relative humidity. No correlation of mold count with either wind velocity or wind direction was discernible. No sampling was done during periods of precipitation, but a few plates exposed immediately following rains yielded few or no colonies.

The counts at each of three sites are seen to vary independently of each other except in the case of *Alternaria,* where the counts at A and B

(both outdoors) during the period of August to December were closely parallel. During this time, however, the count at C (indoors) was zero. The high *Streptomyces* totals were caused in part by "showers" of spores on July 22 and September 2 at Site B. *Alternaria* also had a high count

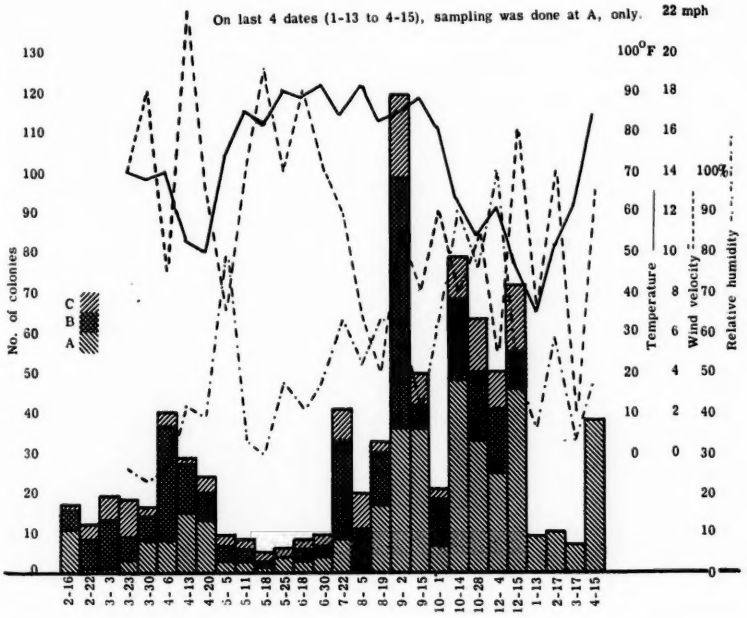


Fig. 1. Total mold count (cumulative for three sites); temperature; wind velocity; relative humidity, 1953-54.

at B on September 2, while *Hormodendrum* showed three such days at A: October 14, October 28, and April 15. It should be noted however, that *Hormodendrum* was all but absent on April 13 and 20 of 1953.

## DISCUSSION

It should be pointed out that, owing to the irregularity and relative infrequency of sampling in the present study, the results cannot be regarded as statistically significant. However, the data are presented as a preliminary and qualitative account of the low altitude aerial mycoflora of this area.

In a comparison of total counts at each site (Table 1) it is seen that 399 isolates occurred at A, 288 at B, and only 142 at C, which was the indoor station. Although site A was in a rural area where there was more vegetation, the difference between A and B is not so great as is at first apparent in the table, since sixty-four of the colonies at A were obtained

on the four sampling dates from January 13 to April 15, during which period sampling was carried on only at this site. Omission of this number leaves a total of 335 for A.

Since site A was located in the immediate vicinity of the Naval Air Station, where the weather data were obtained, it might be expected that these data would bear closer relationship, if any, to the Chamblee samples than to those taken in Atlanta. The count, especially at site A, appears to have a rough inverse relationship to temperature and a direct relationship to relative humidity. However, all three factors may be simply a reflection of seasonal variation, without causal connection. Highest counts were obtained in the fall, with a secondary peak in March and April. These findings further support the concept that there is a seasonal pattern in the occurrence of mold spores in the air, although this pattern is by no means constant for different localities.

There appeared to be no remarkable differences in the type of molds found at the varying sites. As was to be expected, the total count outdoors was greater than indoors (B vs C). Likewise, there were somewhat fewer genera represented at C.

Durham,[2] in 1942, pointed out that *Alternaria* and *Hormodendrum,* together with the spores of stem rust, were outstanding among airborne fungi both in numbers and in widespread geographic distribution. His gravity slides showed *Hormodendrum* counts about twice those of *Alternaria* in Atlanta air. In the present studies the total count of the former was slightly greater than that of the latter but *Alternaria* appeared on a much greater proportion of the sampling days. The two were almost equal in frequency of dominance. The occurrence of one or both of these molds in large numbers in the air over widely varying localities has been reported in a number of other papers, including those of Negroni and Daglio[7] (La Plata, Argentina), Hyde and Williams[6] (Cardiff, Wales), Schaffer, Seidmon, and Bruskin[9] (New Brunswick, New Jersey), and Collier and Ferguson[1] (Brunswick, Georgia).

One of the most notable features of the present study has been the consistently high prevalence of *Streptomyces,* of which only one colony was reported by Collier and Ferguson and which has rarely appeared in other reports. *Hormodendrum* (including *Cladosporium)* also appears to be more important in the Atlanta area than in Brunswick. On the other hand, *Aspergillus* and *Penicillium,* which occupy positions of dominance in the Brunswick studies and elsewhere, were of relatively minor significance in Atlanta, while *Monilia,* which was found only once in this survey, occurred frequently in Brunswick. However, with the important exception of *Streptomyces,* the top ten genera found here are, for the most part, the same as those usually reported most prevalent in other localities.

The appearance of *Curvularia* in the air consistently and in large numbers is a phenomenon not common in previous surveys, wherein this genus is rarely mentioned. It is possible that this organism has been confused

with *Helminthosporium,* which it closely resembles, although the latter has not been very prominent either.

The substitution of Czapek-Dox agar for PDA in the sampling plates following the first few exposures served both to hasten and to facilitate generic identification. Czapek-Dox agar effectively suppresses bacterial growth and permits only sparse vegetative development of molds, while early sporulation is stimulated, so that identification is usually made quickly and positively on the basis of microscopic structure. However, macroscopic differentiation of colonies on this medium is difficult. The growth of mucoraceous molds *(Rhizopus, Mucor)* is greatly restricted, which serves to prevent their masking other colonies as occurs on PDA and other media, but this fact undoubtedly also contributes to the low counts (five and four isolates, respectively) found for these genera. Similar results are reported by Swaebly, Christensen, and Grahek[10] following a comparative study of various media for the collection and identification of airborne molds. These authors found that a modified Smith-Humfield agar, which, like Czapek-Dox, contains no organic nitrogen, markedly restricted the growth of *Rhizopus* and *Mucor* but gave the greatest total colony counts and rated high in ease of identification. On the basis of conformity to the general seasonal pattern of occurrence, and as a result of several direct comparisons between the Czapek-Dox and PDA media, it is believed that any inconsistency introduced into the comparative counts on account of the substitution is not of great magnitude. When plates of the two media were exposed in parallel on various occasions there was found a strong quantitative correlation in the counts, while the qualitative differences (excluding the mucoraceous colonies) were neither great nor consistent. A single colony of *Sporotrichum,* not included in Table I, was obtained on a PDA plate exposed in parallel with the tabulated Czapek-Dox plate on February 17, 1954.

## SUMMARY

1. Air samples at three sites in the vicinity of Atlanta, Georgia, were taken by the "gravity plate" method on Czapek-Dox and potato dextrose agar at weekly to monthly intervals over a period of fifteen months in 1953-54. The 829 mold colonies isolated at all sites, except for twenty-one which consisted of sterile mycelium, fell into a total of forty-nine genera. Extramurally, higher counts were obtained in a rural than in an urban area and the number of isolates at each of these sites greatly exceeded the comparable urban intramural count.

2. Consistent dominance was displayed by the genera *Streptomyces, Alternaria,* and *Hormodendrum* according to three criteria: total isolates, frequency of appearance, and frequency of dominance on any given day. *Penicillium* and *Aspergillus* were of relatively minor importance. The counts of *Streptomyces* and *Curvularia* were notably high in comparison with those appearing in reports from other geographical areas. With the

exception of a single colony of *Aspergillus fumigatus* no infectious pathogens were recovered.

3. There was a distinct seasonal variation in the total count and in the counts for each of the dominant organisms.

4. An organism apparently new to this country, *Tricellula inaequalis* (van Beverwijk) 1954, was collected on two occasions, each at a different site. The only previously reported isolate of this genus and species was obtained from the air in Norway.

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The author is indebted to Mr. Everett Priest for his invaluable aid in the preparation of the graph in Figure 1. Appreciation is expressed also to Professor F. A. Wolf for his identification of *Pseudoplea gaumanni* and to the Aerology Office, U. S. Naval Air Station, Chamblee, Georgia, for supplying the weather data.

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"I have been speculating last night what makes a man a discoverer of undiscovered things; and a most perplexing problem it is. Many men who are very clever—much cleverer than the discoverers—never originate anything. As far as I can conjecture, the art consists in habitually searching for the causes and meanings of everything which occurs."—Darwinisms.

# TREATMENT OF PRURITIC DERMATOSES WITH CHLORPHENIRAMINE MALEATE AND PREDNISONE IN COMBINATION (METRETON)

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DURING my use of antihistamines developed during the past ten years, I have found that 75 per cent of patients with allergic and pruritic dermatoses show major improvement of their itching, while 20 per cent improve to a moderate degree, when treated with chlorpheniramine maleate (Chlor-Trimeton Maleate®). I have previously reported that an injection and repeat action tablets containing this substance give prompt and sustained symptomatic relief in pruritic dermatoses.[1,2]

Receptive to the idea that a new drug or combination might offer an opportunity for obtaining an even better result in the treatment of pruritus in various skin diseases, a study was undertaken of Metreton® tablets. Metreton combines in a single tablet 2 mg of the antihistamine chlorpheniramine maleate (Chlor-Trimeton) with 2.5 mg of prednisone (Meticorten) and 75 mg ascorbic acid.

Prednisone is one of the newest steroids with adrenocortical activity. Closely related in structure to cortisone and hydrocortisone, it has proved highly effective as an antirheumatic and anti-inflammatory agent.[3,4] Its antiallergic and anti-inflammatory properties have been demonstrated by systemic administration in a variety of skin diseases.[5-10] The combination of chlorpheniramine with prednisone in Metreton offers antihistaminic, anti-inflammatory, and antiallergic action in a single preparation. It seemed that this should prove advantageous in the treatment of severe pruritic and allergic disorders of the skin where an antihistamine alone might not provide complete relief.

## CLINICAL STUDY

During the past ten months, eighty-seven patients with pruritic dermatoses were treated with Metreton* tablets. Patients were selected who had been treated elsewhere for two months or longer without satisfactory result or whose pruritus associated with the skin disease had not responded, or had responded incompletely, to antihistaminic therapy. Thus, no patient in the series was treated at the onset of his skin disorder. In each new patient the usual treatment with Chlor-Trimeton repeat action tablets or injection, or both, was tried first.[1,2] This provided a more stringent test of

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Read at the meeting of the Metropolitan Dermatological Society of Chicago, November 14, 1956.

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*Furnished by George Babcock, Jr., M.D., Division of Clinical Research, Schering Corporation, Bloomfield, New Jersey.

the efficacy of Metreton because only the more severe and partially relieved cases were placed on this therapy.

The ages of the patients ranged from nine to eighty-three years. The dermatoses and the numbers of patients with each were as follows: circumscribed neurodermatitis, twenty-two; disseminated (atopic) neurodermatitis, nine; contact dermatitis, thirty; pruritus universalis or anogenitalis, thirteen; urticaria, eight; miscellaneous pruritic dermatoses, two; and lichen planus, herpes zoster, and erythema multiforme, one each.

Because these tablets contain prednisone, the same precautions were used as are advised in the use of the steroid alone. Before treatment a careful history was taken and each patient examined to exclude the presence of diabetes mellitus, severe hypertension, peptic ulcer, tuberculosis, renal insufficiency, and mental disorders. The weight, blood pressure, and findings upon urinalysis were recorded.

The actions of chlorpheniramine and prednisone are complementary and additive. Therefore, only small doses of the combination were given to the patients in this series with severe pruritic diseases of the skin. The average initial dosage was four tablets daily. Two tablets were given after breakfast and two after approximately a twelve-hour interval, usually upon retiring. The patients were customarily seen once a week. They were questioned carefully as to new symptoms and any observations they might wish to offer.

Advice was given concerning diet, that is, to reduce the consumption of coffee, tea, alcohol, seasonings, and spices. However, no restriction was imposed upon the sodium chloride intake. Mineral oil or a detergent was substituted for soap in cleansing the skin. For local application, the patients were given a mild ointment containing 2 per cent boric acid solution 40 gm; lanolin or Aquaphor® 40 gm, and white petrolatum to make 100 gm, or wet dressings of 2 per cent boric acid solution or 1:20 Burow's solution, if there were exudative lesions.

## RESULTS OF TREATMENT

The relief of pruritus afforded by Metreton tablets became apparent rapidly and was sustained for a period of eight to twelve hours. In 85 per cent of the patients the pruritus completely subsided within a few days or weeks. Improvement continued gradually and it was ultimately possible to administer a lower dosage for the maintenance of a satisfactory result.

The accompanying table gives the over-all results. An excellent response, with 85 to 100 per cent relief of inflammation or pruritus, or both, was obtained in forty-nine patients. The result was good, that is, 70 to 85 per cent improvement occurred, in twenty-eight patients. Eight patients showed a moderate degree of improvement (50 to 70 per cent). In two patients, no benefit beyond that already obtained with chlorpheniramine alone became apparent during treatment with the combined preparation.

In the majority of the patients, four of the new tablets daily sufficed to

TABLE I. RESULTS OF TREATMENT WITH METRETON

| Diagnosis | No. Patients | Effect | | | |
|---|---|---|---|---|---|
| | | Excellent | Good | Moderate | None |
| Dermatitis, contact | 30 | 18 | 9 | 2 | 1 |
| Erythema multiforme | 1 | 1 | — | — | — |
| Herpes Zoster | 1 | 1 | — | — | — |
| Lichen ruber planus | 1 | — | — | 1 | — |
| Neurodermatitis, circumscribed | 22 | 12 | 8 | 2 | — |
| Neurodermatitis, disseminated (atopic) | 9 | 4 | 4 | 1 | — |
| Pruritus universalis or anogenitalis | 13 | 9 | 2 | 1 | 1 |
| Urticaria, acute or chronic | 8 | 3 | 4 | 1 | — |
| Miscellaneous pruritic dermatoses | 2 | 1 | 1 | — | — |
| Total | 87 | 49 | 28 | 8 | 2 |

ameliorate the symptoms of burning and itching. Six per cent of the patients required six tablets daily to obtain a beneficial degree of improvement. Two patients, one with contact dermatitis and one with pruritus anogenitalis, obtained no more relief with a dosage of six Metreton tablets daily than with three 8 mg repeat action chlorpheniramine tablets which had previously been used. A larger dosage might possibly have been more effective. However, no patient in the study received more than six of the new tablets daily for the suppression of symptoms and no injections were given. In most instances the daily dosage could gradually be reduced by decrements of one tablet until the minimum maintenance dosage was reached. When possible thereafter, the medication was discontinued.

In these cases of acute or chronic, severe, but nonfatal, pruritic skin diseases, the combination of chlorpheniramine with prednisone had the advantage of producing a more rapid and better response than was obtained in previous studies with the oral and injectable forms of this antihistamine alone.

No side effects were noted, even though some of the patients required a maintenance dosage for two to three months. As in former studies with chlorpheniramine, a few patients experienced a feeling of tiredness during the day. These patients, and one patient who noted drowsiness when taking two tablets after breakfast, had a good clinical result with a dosage of two tablets upon retiring. No edema, hypertension, glycosuria, or gain in weight was noted.

## CASE REPORTS

The following case summaries illustrate the results:

*Case 1.*—S. N., a seventeen-year-old boy, had disseminated neurodermatitis of many years' duration, with severe itching, marked lichenification and pigmentation of the affected areas of the face, neck, trunk, and arms. He had been under medical care elsewhere for three years. For one week this patient received chlorpheniramine repeat-action tablets and injection. The severe itching failed to subside. Consequently, the medication was changed to four Metreton tablets daily. The application of boric acid ointment was continued. The following week, the patient was sleeping better, the itching was less pronounced, and the many excoriations

had begun to heal. He received four Metreton tablets daily for three weeks, two tablets daily for two weeks, one tablet daily for one week, and then was able to discontinue the medication after a total dosage of 120 tablets (240 mg chlorpheniramine and 300 mg prednisone). The itching gradually ceased, the excoriations healed, and the skin became softer and smooth.

*Case 2.*—R. V., a fifty-three-year-old man, who had been a horticulturist for years, had had recurrent attacks of severe pruritus and dermatitis of the arms and legs for two years. In June, 1955, he had a severe vesicular dermatitis of the hands and legs down to the toes, and erythema of the face, and could walk only with great difficulty and pain. He was hospitalized for eleven days and treated with corticotropin in 500 cc of 5 per cent glucose solution in water by continuous intravenous infusion over an eight-hour period, the initial dosage being twenty units. A total of 170 units was given. The blood count and the results of blood chemistry studies and urinalysis remained within normal limits. Numerous tests for allergy failed to uncover the cause of the patient's illness. Although he improved sufficiently to leave the hospital, the symptoms continued in lesser degree for many months. The patient was treated with various local applications and oral, parenteral, and topical corticotropin and corticosteroid preparations in order to enable him to walk and work, albeit with difficulty. Beginning on October 17, 1955, the patient received four Metreton tablets daily and used boric acid ointment and dressings. After one week of this treatment, there was less itching and no new efflorescences. The skin had improved in appearance. Exudation on the feet had stopped. The patient had been forced to wear sandals for months. Metreton was continued for one month with four tablets daily, then two tablets daily, and finally one tablet daily, for a total of 240 tablets (480 mg chlortrimeton and 600 mg prednisone) without the appearance of side actions. The patient was examined every two weeks until January, 1956. His skin regained a normal appearance and he was able to work in a conservatory and in his own garden. In June, 1956, the patient reported that, when he occasionally noticed some itching or burning of the skin, it could be relieved with the ingestion of two Metreton tablets. He has remained well and was last seen in October, 1956.

*Case 3.*—R. M., a sixty-one-year-old man, had herpes zoster of the right shoulder and dorsal area of the right arm of two days' duration. He was unable to work because of severe pain. Three days' treatment with Pituitrin®-S injections was followed by spreading of the disease and pain. Metreton was then tried in a dosage of two tablets twice daily. The patient noted less pain and burning of the affected areas after two days. After two weeks' treatment, the skin had healed and was dry. The pain had disappeared.

## SUMMARY

Eighty-seven patients with severe pruritic dermatoses were treated with Metreton, a combination of chlorpheniramine with prednisone and added ascorbic acid, which produced an effect superior to that obtained with chlorpheniramine repeat-action tablets alone or in combination with chlorpheniramine injection. In 88.5 per cent of this series of patients with acute or chronic pruritic skin diseases on short-term or long-term therapy, 70 to 100 per cent relief of symptoms occurred. Itching and exudation were relieved soon after the first dose was administered—sometimes over night in patients who had suffered for a month or more and had been unresponsive to other treatment. The action of the antihistamine and antiallergic

actions of the steroid are additive and complementary. Therefore, a small dosage was usually adequate. The average initial dosage in the majority of the patients was four tablets daily. With improvement the dosage could gradually be reduced and often discontinued.

Metreton caused no sodium or water retention nor elevation in blood pressure, thus, there was no need for salt restriction during its use. Our study failed to demonstrate any serious undesirable side effects.

## CONCLUSIONS

Therapy with Metreton tablets, consisting of prednisone combined with chlorpheniramine and ascorbic acid, constitutes a different and effective approach to treatment of patients with itching skin diseases. It shows great promise in patients commonly seen in everyday practice on an ambulatory basis. The results of the study indicate the combination is safe in the recommended dosage and valuable in many cases of pruritic diseases for the prompt and marked improvement.

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# CONTROLLED STUDIES OF TOPICAL MEDICATIONS IN NASAL ALLERGY

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A CERTAIN percentage of patients given any medication will be found to be placebo reactors; i.e., they will react to an inert or inactive substance. It is of distinct importance, therefore, in the evaluation of medications in allergic patients to determine in any study whether or not placebo reactors are included. Too often glowing preliminary reports of nasal medications later cannot be substantiated. In recent years, the use of antibiotics and steroid hormones topically in the nose has been of considerable interest, and this has resulted in much investigative work.

We are all familiar with the use and effect of both the antibiotics and steroid hormones when used systemically. The question of possible benefits when these preparations are used topically requires careful consideration and analysis.

Any studies of this type must be adequately controlled, in order to eliminate errors of interpretation which may be due not only to the enthusiasm of the investigators, but also to other factors which may color or influence the results. Therefore, it seems to us that any medication under study must be compared with a placebo. Also, the investigators themselves should not know the contents of the preparations used.

Many workers agree that vasoconstrictor solutions used in the nose for prolonged periods may in themselves cause so-called "rebound" turgescence. For this reason, many patients are completely addicted to the use of nose drops or sprays. The avoidance of such solutions has helped many patients.

The purpose of this presentation is to describe briefly certain experiences in controlled studies of nasal medications which have been done over a ten-year period.

## TYROTHRICIN

A controlled study of 179 patients using tyrothricin was done at Charity Hospital in New Orleans in 1945 and 1946 by one of us (H.D.O.). Tyrothricin contains two antibiotics, gramicidin and tyrocidine. The purpose of the study was to determine whether acute flareups of allergic symptoms could be benefited by the control of respiratory infections with

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the help of tyrothricin. It is of course recognized that infections of this type may aggravate various allergic conditions.

The lateral head-low position was used. Neither patients nor investigators were aware of the contents of the various solutions. It was found that the tyrothricin-treated group was not benefited when compared to the placebo-treated group. No evidence of sensitization was observed. Both preparations were used four times a day at the onset of symptoms.

In this study one solution contained tyrothricin 0.02 per cent and propadrine 1.5 per cent.* The other solution, the control, contained only the propadrine.

No attempt was made to distinguish between "colds" due to infections and simple flareups of allergic manifestations. Therefore, it was concluded that the benefits that were recorded in this study were merely compatible with those ordinarily noted after the use of a vasoconstrictor in the nose.

### FIRST BACITRACIN STUDY

In 1948 a similar study was made using bacitracin combined with a vasoconstrictor; the placebo was a vasoconstrictor alone. This work was done with Drs. Florence Evans and J. D. Kelly.

Patients in the treated group were given nose drops containing bacitracin solution** 200 u/ml with 0.5 per cent ephedrine hydrochloride. Myristyl-gamma-picolinium chloride was present in a proportion of 1:10,000. The pH of the solution was approximately 6. Irritation and stinging appears when the concentration of the bacitracin is greater than 200 u/ml. Solutions that were given to the control group contained racephedrine hydrochloride 1 per cent in Ringer's Solution. The same directions were given to the patients in this series that were given to those in the previous tyrothricin study, and the same questionnaire was used.

Nasal cultures were made prior to treatment on all patients, and again at the conclusion of the study in many patients. Routine antral irrigations or punctures for culture purposes were done in the beginning, but had to be discontinued for various reasons, including the vigorous objections of the patients.

Material was collected from the region of the turbinates with a sterile cotton swab and streaked immediately on 10 per cent human blood agar, the base of which was heart infusion agar (Difco) with 2 per cent proteose peptone (Difco) added. A piece of filter paper soaked in a solution of bacitracin containing 20 u/ml was dropped on the area of the plate most heavily inoculated. These cultures were incubated at 37° C and examined after twenty-four hours, forty-eight hours, and seven days. Zones of sensitivity were determined as areas free of growth surrounding the filter paper. The amount of growth obtained from these cultures

*Materials supplied by Sharpe & Dohme, Inc., Philadelphia, Pennsylvania.
**Materials supplied by the Upjohn Company, Kalamazoo, Michigan.

ranged from heavily crowded plates to those having no growth or only a few colonies on the entire plate. On these latter plates, the sensitivity of the organisms was not easily determined. The organisms that were found and their sensitivity to bacitracin are shown in Figure 1.

IN VITRO SENSITIVITY TO BACITRACIN

| ORGANISM | SENSITIVE TO BACITRACIN | NOT SENSITIVE TO BACITRACIN | SENSITIVITY * NOT DETERMINED | TOTAL |
|---|---|---|---|---|
| DIPHTHEROIDS | 29 | 0 | 6 | 35 |
| STAPHYLOCOCCUS GROUP | 22 | 30 | 39 | 91 |
| GAFFKY-SARCINA AND NEISSERIA | 13 | 0 | 2 | 15 |
| STREPTOCOCCUS GROUP | 7 | 1 | 4 | 12 |
| GRAM NEGATIVE BACILLI | 0 | 4 | 1 | 5 |
| GRAM NEGATIVE PLEOMORPH | 9 | 2 | 1 | 12 |
| TOTAL | 80 | 37 | 53 | 170 |

* ON CERTAIN CULTURES THE GROWTH OF ORGANISMS OCCURRED SO SPARSELY THAT SENSITIVITY COULD NOT BE DETERMINED ON PRIMARY CULTURE. SUB CULTURES WERE NOT DONE FOR SENSITIVITY.

Fig. 1

Statistical analysis of these results was done by Dr. Huldah Bancroft. Her conclusion was that the Chi Square test of these data shows that the difference in distribution is not due to chance. P is much less than 0.01. Therefore, the difference in sensitivity is a real difference.

Diptheroids were found in an unusually high percentage. This may be due to the fact that a very rich media was used, and incubation was carried out for seven days. Usually more than one organism was found on each culture.

In this study, eight white patients received bacitracin while ten were in the control group. More symptoms were found in the bacitracin-treated group; however, it was felt that inadvertently there were more severe cases included in the bacitracin-treated group.

In the larger group of Negro patients (with twenty-three patients in each group), there was a definite tendency toward a lessening of symptoms in the bacitracin-treated group. However, these figures were not significant. Sensitization was not observed. Also it should be pointed out that, although the average duration of symptoms among individuals having bacitracin-sensitive organisms was lower than for those having organisms not sensitive to bacitracin, the difference was not significant.

### SECOND BACITRACIN STUDY

In 1949, another controlled study of the topical use of bacitracin in the nose was done with Louis Cullick. Some evidence of lesser symptoms in the bacitracin-treated group was observed.*

From these studies it may be inferred that bacitracin may be of some benefit in the allergic individual. As stated above, our purpose was only to determine if allergic manifestations could be helped by the control of respiratory infections. It had been amply demonstrated by many workers that the topical use of bacitracin in other areas is effective in the presence of infection.

### HYDROCORTISONE ACETATE STUDY

In 1954, another study with Bancroft, Ruli, Stevens, Branson and Bodet was made using 1.5 per cent hydrocortisone acetate in plastic spray bottles in patients with various types of nasal symptoms.* This study did not deal primarily with its effect in infection but we were interested in the relief that could be obtained in those individuals with various types of nasal complaints. As in the other studies, we included patients in a large outpatient clinic at Charity Hospital in New Orleans (all of whom had recurrent nasal symptoms), and an attempt was made to evaluate their response to the hormone from both an objective and subjective viewpoint.

All patients had complaints suggestive of allergic rhinitis. The diluent used consisted of polysorbate propylene glycol, sodium chloride, quatresin, glyceryl monosterite, spermaceti, and deionized water. Two solutions "A" and "B" were used. To one of these, hydrocortisone acetate 15 mg per cc (1.5 per cent) was added. Throughout the entire study none of us knew which solution contained the hydrocortisone; therefore, the study was completely "blind." Vasoconstrictors, antithistamines or antibiotics were not used.

Sensitization to the preparation was not observed, and there was no indication of systemic absorption.

Careful statistical analysis of the findings revealed some slight degree of benefit in the hydrocortisone-treated group as compared with the control group. However, it should be noted that the patients were instructed to use two "squirts" of the preparation in each nostril five times daily. In the light of our later findings, this amount failed to give the desired initial heavy tissue saturation. We feel that if the same study were repeated (using the method to be described below) the results would possibly be significant.

It is noteworthy that many of the placebo-treated patients reported benefit. This again emphasizes the fact that any study of this type should be adequately controlled.

*Materials supplied by the Upjohn Company, Kalamazoo, Michigan.

### PREDNISOLONE STUDY

In 1955, a blind placebo-controlled study was undertaken at the allergy Clinic of the New Orleans Eye, Ear, Nose and Throat Hospital to evaluate the effectiveness of prednisolone* when topically applied to the nasal mucosa in the form of a spray.[1]

Stringent criteria were established for inclusion of a patient in the investigation. These included positive nasal eosinophilia, positive family and childhood history, the presence of confirmatory skin tests, and the presence of typical findings of nasal allergy on rhinoscopy. Thirty patients fulfilling these requirements were selected, and taken off all medication and hyposensitization therapy prior to the administration of the trial material.

Three preparations, labeled A, C, and D, were supplied by the manufacturer; the composition of the contents of the plastic spray bottles was unknown to the investigators until the study was completed. Every patient received all three of the preparations during the course of the study, each being used for a period of one week; an interval of one week without treatment was interposed between these periods of usage in order to eliminate any possible carryover effect of previous therapy.

The material was applied by what we have come to term the "initial tissue saturation method," which consists of frequent application of the material to the nasal mucosa for a period of two days in order to build up a high initial tissue saturation. This technique was used because adequate treatment with corticosteroids requires the establishment of high levels of the hormones in the tissues. It can be assumed that such tissue concentration can be achieved by topical application because of the excellent absorptive capacity of the nasal mucosa. Patients were directed to use one "squirt" in each nostril every hour for the first two days while awake, and four times a day thereafter.

In order to determine whether prednisolone used in this manner would produce any systemic effects, the effect of the preparation on the circulating eosinophils was studied. Ten patients were selected at random and a total blood eosinophil count was done on each. After using the preparation in the manner described above for a period of three days, the blood eosinophil count was taken again, and it was found that there were no significant changes in blood eosinophilia following usage of prednisolone intranasally by the initial tissue saturation method.

During the period in which this investigation was being conducted, there was no significant variation in the atmospheric pollen count nor in the weather conditions in New Orleans which might have accounted for the results obtained.

None of the patients reported improvement following the use of preparation "A." At the conclusion of the study period, the investigators were informed that this preparation was a placebo.

*Materials supplied by the Upjohn Company, Kalamazoo, Michigan.

Twenty-four of the thirty patients were of the opinion that they obtained most relief as a result of using preparation "C," which contained 0.05 per cent prednisolone. It should be noted that all of these patients also obtained varying degrees of relief from preparation "D," but they reported more relief with preparation "C" than preparation "D." This was confirmed by rhinoscopy. Preparation "D" was found to contain 0.1 per cent prednisolone.

Six of the thirty patients reported that preparation "D" was most effective in relieving their symptoms. They, likewise, reported varying degrees of relief with preparation "C"; however, they indicated that preparation "D" was more effective than preparation "C." It is noteworthy that the patients who reported preparation "D" to be the most effective demonstrated more advanced tissue changes than those who reported that preparation "C" was the most beneficial.

## CONCLUSIONS

1. Proper evaluation of any nasal medication depends upon adequately controlled studies. If the patients are properly divided, factors such as weather, pollen or mold counts, are neutralized.
2. A controlled study of tyrothricin did not reveal any lessening of symptoms due to a better control of respiratory infections.
3. Two similar studies with bacitracin indicated some benefit after the use of this preparation.
4. Hydrocortisone acetate (1.5 per cent) was found to lessen allergic complaints in some individuals; however, it should be pointed out that the initial tissue saturation method was not used.
5. Using prednisolone in two strengths by the initial tissue saturation method, beneficial results were obtained in thirty patients; while no results were obtained in a control group similarly treated.

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"The time is coming when the practice of medicine will rest securely upon a firm scientific foundation, upon a systematic understanding of the life-processes in all their complexity, and no longer upon the insecure and shifting basis which partially supports it today, with clear understanding in part, but with a great mass of uncoordinated, empirical data necessarily as the main reliance."—VANNEVAR BUSH, *Professional Collaboration* (Science, 125:49, 1957)

# EVALUATION OF CHOLINE THEOPHYLLINATE IN THE MANAGEMENT OF CHRONIC ASTHMA OF CHILDHOOD

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DRUGS containing theophylline are known to be useful in the control of chronic asthma in childhood[1]; however, the necessity for parenteral or rectal administration to avoid gastrointestinal difficulties sharply limits the applicability of the xanthines. Choline theophyllinate for oral administration was submitted for evaluation on the basis of adequate blood theophylline levels without gastric irritation, particularly in children with chronic asthma requiring long-term treatment. This report outlines experience with the drug in a group of institutionalized chronic asthmatic children.

The literature on choline theophyllinate (Choledyl® Nepera) indicates that this new oral theophylline agent does not produce gastric irritation[2] can be given for long periods of time without loss of effect,[3] prevents the occurrence of bronchospasm,[4] is highly soluble,[5] and produces therapeutically adequate theophylline blood levels.[6]

Reported clinical experiences indicate that choline theophyllinate is an effective tool for the treatment of bronchial asthma.[7] Brown[8] showed this agent as being most effective in older nonallergic emphysematous patients. Recently, Simon[9] reported that choline theophyllinate was more effective than aminophylline in the maintenance of geriatric patients with chronic pulmonary conditions, and that it was markedly effective in minimizing the typical symptoms of coughing, dyspnea, etc. This drug, however, had never been studied previously in a pediatric population.

Evaluation of this drug was carried out according to the techniques of Tuft and Kraus[10] in which each case acts as its own control. Long periods of "around the clock" observations provide reasonably accurate impressions of the basal state of each individual patient. This *constant* observation makes it possible to use each child as his own control: his clinical status is fully understood and can be followed *before, during,* and *after* treatment with a new agent. In addition, the known pattern of the disease enables the observer to determine quickly the effect of a drug and the lack of effect of a placebo. Trials can be continued over extended periods of time. If the drug under evaluation is effective, the pattern of the disease can be altered almost at the will of the observer.

A group of eighty children from five to sixteen years of age was used to study this drug. Their routine medication was not changed in any respect except for the addition of choline theophyllinate. None had received any theophylline-containing medication for at least one month

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prior to the start of this study. A dosage of one tablet (200 mg) four times a day was employed in all instances.

Clinically, these patients suffer from wheezing, coughing and dyspnea during certain periods of each day or night. When choline theophyllinate was included in therapy, approximately sixty per cent were controlled to the extent that wheezing and coughing disappeared completely. Improvement in those cases responding favorably occurred within four to five days. Another twenty-five per cent derived some benefit but were not sufficiently improved to warrant continued administration of the drug. Fifteen per cent of the patients derived no additional therapeutic benefit from this compound.

When administration of choline theophyllinate was discontinued at the end of four to six weeks of therapy, symptoms gradually began to reappear so that at the end of one week the previously controlled children demonstrated all of their original symptoms. In some cases, placebos were given after the "rest period" with no therapeutic benefit.

The incidence of gastrointestinal symptoms was nil. There was no complaint of nausea, vomiting or abdominal pain on the part of any patient in this series.

The results of administration of choline theophyllinate compare favorably with those obtained in the institution by the use of aminophylline in the form of sustained release tablets. This oral dosage form avoids the gastrointestinal difficulties as well, but is not available commercially.

The lack of gastrointestinal symptomatology in all of these patients makes choline theophyllinate a valuable agent in the treatment of chronic bronchial asthma in childhood. This is particularly of interest since the dose given is the usual starting adult dose, thus emphasizing that the usefulness of this compound is not impaired by gastrointestinal irritation as with the customarily used theophylline and aminophylline compounds. Theophylline blood levels were performed on ten patients of this series. The levels, which will be reported in detail elsewhere, were generally lower than those obtained by Gagliani and associates[6] but occurred with regularity after a given dose. On the other hand, absorption of aminophylline suppositories has been reported to be erratic as well as dangerous.[11] This study demonstrates that choline theophyllinate fulfills the criteria for acceptability in that it produces satisfactory therapeutic results without side effects and, therefore, represents a valuable addition to our therapeutic armamentarium in the therapy of chronic asthma of childhood.

## SUMMARY

Oral choline theophyllinate was administered to a group of eighty children between the ages of five and sixteen years, all of whom had severe chronic asthma. The drug controlled completely the wheezing and dyspnea in sixty per cent of these chronically ill children without gastric irritation.

As a result, the drug is now used routinely in all children with chronic asthma.

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## THE METHODS OF ACQUIRING KNOWLEDGE

There are two methods in which we acquire knowledge—argument and experiment. Argument allows us to draw conclusions, and may cause us to admit the conclusion; but it gives no proof, nor does it remove doubt, and cause the mind to rest in the conscious possession of truth, unless the truth is discovered by way of experience, e.g., if any man who had never seen fire were to prove by satisfactory argument that fire burns and destroys things, the hearer's mind would not rest satisfied, nor would he avoid fire; until by putting his hand or some combustible thing into it, he proved by actual experiment what the argument laid down; but after the experiment has been made, his mind receives certainty and rests in the possession of truth which could not be given by argument but only by experience.—ROGER BACON (1214-1294).

# SKIN REACTIVITY IN HYPERSENSITIVITY SYNDROME OF A MOUSE

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SINCE 1947, the author and his collaborators have described, in a series of papers, different phases of hypersensitivity in mice immunized with pertussis vaccine.[1,2] Such mice are more resistant to invasion by *Hemophilus pertussis* and displayed the features of specific, anaphylactic shock by this antigen, as well as nonspecific hypersensitivity, histamine shock and greater susceptibility to unrelated infections. In the present communication we wish to report our recent observations on the reactivity of the skin in hypersensitive mice.

## METHOD

For sensitization, Carworth mice, strain CFW, similar to those used previously, were injected intraperitoneally on two successive days with *H. pertussis* vaccine (7.5 billion cells). After seven days the mice were tested for skin sensitivity to histamine and to pertussis antigen. We selected as an antigen pertussis nucleoprotein (NPD), since this material is soluble and produced anaphylaxis when injected intraperitoneally in sensitized mice. For skin testing the mice were clipped, and each was injected intradermally on one side of the back with 0.05 ml of a mixture of saline and India ink (dil. 1:6); on the other side with the same mixture containing 0.02 mg of nucleoprotein or 0.01 mg of histamine diphosphate. Some mice were injected on both sides of the back with ink saline mixture. On the day following the injections the mice were killed and skinned, the skin being stretched out and allowed to dry overnight. The ink spots were then measured with calipers to determine the area of the spreads. The average areas for each group of mice are given in Table I. Table II presents a statistical analysis of the data.

## RESULTS

The spread of NPD in sensitized mice showed a large increase in area compared with that in nonsensitized mice [ (a) vs. (c) ]. The spread of histamine in sensitized mice was even greater [ (f) vs. (h) ]. As shown by the increase in area of the saline ink spots in sensitized mice receiving NPD on the other side of the body, compared with the area of the saline ink spots in sensitized mice receiving no NPD [ (d) vs. (e) ], the skin of sensitized mice allowed the "diffusion" of NPD from one side of the body to the other.

The same results were obtained with histamine.

TABLE I. AREAS OF SPREADS OF INDIA INK IN SENSITIZED AND NON-SENSITIZED MICE

| | NPD Spread | | | | Saline Spread | Histamine Spreads | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Normal Mice | | Sensitized Mice | | Sentized Mice | Normal Mice | | Sensitized Mice | |
| | NPD | Saline | NPD | Saline | Saline | Hist. | Saline | Hist. | Saline |
| No. of cases | 12 | 12 | 47 | 47 | 12 | 11 | 11 | 10 | 10 |
| Average area of spread, $cm^2$ | 0.709 | 0.745 | 2.23 | 1.33 | 0.965 | 0.869 | 0.675 | 4.00 | 1.67 |
| Designation of groups for statistical analysis | (a) | (b) | (c) | (d) | (e) | (f) | (g) | (h) | (i) |

TABLE II. STATISTICAL ANALYSIS OF DATA

| Groups compared with each other | Type of comparison* | Analysis | p |
|---|---|---|---|
| t test (a) vs. (b) | paired test | difference not significant | — |
| t test (c) vs. (e) | paired test | difference significant | $p<0.001$ |
| t test (d) vs. (e) | non-paired test | difference significant | $p<0.02$ |
| t test (a) vs. (c) | non-paired test | difference significant | $>0.01$ |
| t test (f) vs. (g) | paired test | difference significant | $p<0.001$ |
| t test (h) vs. (i) | paired test | difference significant | $p<0.05$ |
| t test (f) vs. (h) | non-paired test | difference significant | $>0.02$ |
| t test (g) vs. (i) | non-paired test | difference significant | $p<0.001$ |
| | | | $p<0.001$ |

*Paired test = comparison of tests performed on same animal.
Non-paired test = comparison of tests performed on different animals.

## DISCUSSION

The counterpart of the increase of skin reactivity in mice hypersensitive to *H. pertussis* vaccine is found in papers by several authors, who have reported that children vaccinated with whooping cough vaccine also became skin positive to intradermal injection of homologous antigen.[3-5] These authors did not suspect that this phenomenon could be due to a sensitization, although they compared skin reaction with the immunity in children. Coexistence of immunity and hypersensitivity after injection of pertussis vaccine in a mouse was stressed by Pittman.[6] This phenomenon could lead to a discrepancy in the evaluation of the skin test. For instance, after immunization of children by diphtheria toxoid, a positive skin test (using toxoid) indicated acquired sensitivity to diphtheria protein (Maloney test), while the negative Schick test (using toxin) expressed immunity (i.e., increase of resistance to toxin).

In our own work we were able to differentiate these two phenomena after injection of pertussis vaccine into mice. Immunization of mice by

pertussis vaccine increases their resistance to invasion by homologous organisms and induces hypersensitivity; the latter could be demonstrated by: (a) anaphylactic shock with antigen, (b) histamine shock, (c) increase of nonspecific susceptibility to unrelated infections.[7-10].

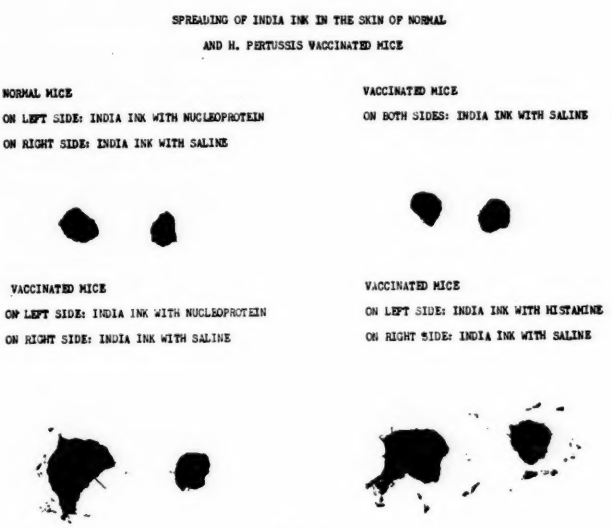


Fig. 1.

In our present studies we found that both antigen and histamine induced greater spreading of India ink in the skin of sensitized than in normal mice. This increase of reactivity of the skin in mice can be considered as a manifestation of the hypersensitivity syndrome produced by injection of pertussis vaccine. Also, in these experiments we have demonstrated a simple technique for testing nonspecific hypersensitivity. Since the agent responsible for hypersensitivity remains unknown in many cases, an assay method to test skin sensitivity with a nonspecific agent such as histamine might be of help. The use of histamine presents a particular interest because of its supposed role in allergy.

## SUMMARY

We have observed that both homologous antigen and histamine induced greater spreading of India ink in the skin of mice sensitized by pertussis vaccine than they did in normal animals.

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*Yale University School of Medicine*

*Submitted January 21, 1957*

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## PLASTER OF PARIS IN SPASMODIC ASTHMA

Communicated for the *Boston Medical and Surgical Journal.*

Not having noticed anything in the medical works of the day, touching the use of the above-named article, in the treatment of spasmodic asthma, I am led to believe it is not in general use. In my hands it has proved more effectual than any, or even all other remedial agents, in the treatment of asthma.

Some three years since, I was called to see a severe case of this disease in the person of a young lady of 18. After going through with the articles commonly used in such cases, with but little effect, I accidentally hit upon the use of "plaster of Paris," in a mixture, with almost magic-like results. The only thing previous to this, that gave her much relief, was the smoking of stramonium leaves. Since using the plaster, however, she has been constantly improving; in fact, for the last two years or more she has nearly forgotten what formerly alarmed not only herself and friends, but troubled her physicians. I have used this article ever since, with similar results.

About two months since I was called to witness the agony of a little girl of twelve years, lately moved into this vicinity—more to console her friends than to relieve the sufferer, as they had given up the idea of ever seeing her cured or even made better; for, to use their expression, they had "been to all the doctors, and they didn't do her any good." She had not been in a recumbent position for a week. I immediately commenced the use of my favorite remedy, with results as before.

The mixture should be prepared similar to lime water, and used freely, diluted in water or milk, on each recurrence of the spasm.

I am in the habit of prescribing for my asthmatic patients, cold sponging about the neck and chest every morning, followed by brisk friction. The *modus operandi* of this remedy I leave for others to enlarge upon.

J. P. Root, M.D.

New Hartford Centre, Ct., Jan. 13, 1854.

# CLINICAL EVALUATION OF A NEW ANTIHISTAMINIC DRUG

NATHAN SCHAFFER, M.D., F.A.C.A.
East Orange, New Jersey

A NEW antihistaminic drug, Diafen®,* was clinically assayed on ninety-two patients with symptoms primarily of seasonal vasomotor rhinitis due to the pollens of grasses and ragweed.

The chemical composition of Diafen is 1-methyl piperidyl-4-benzhydryl ether hydrochloride. It is a white or slightly off-white crystalline powder, soluble in water, chloroform, alcohol, and only slightly soluble in ether. The melting point is 213° C. It is a member of the class of benzhydryl antihistaminic objects which includes Benadryl®.**

## CLINICAL EVALUATION

*Age and Sex of Patients.*—The ages ranged from one to sixty-eight years.

| | | |
|---|---|---|
| Ages | 1—5 | 4 patients |
| | 6—10 | 16 patients |
| | 11—15 | 15 patients |
| | 16—25 | 25 patients |
| | 26—45 | 26 patients |
| | 46—68 | 6 patients |
| | Total | 92 patients |

Fifty-seven of the patients were female and thirty-five were male.

*Dosage.*—The average dosage of the drug was 2 mg four times daily. Children in the first age group were given 1 mg four times daily, and a few adults were given 4 mg four times daily. The time period covered was from three to seven months.

*Laboratory Findings.*—Urine analyses, blood hemoglobin, and blood differential smears were done on fifty patients selected at random three times during the period of medication. This group included all patients who had symptoms of side reactions. No abnormalities were noted in the routine urine examinations, in hemoglobin content of the blood, or in the differential counts done on blood smears.

## RESULTS

Excellent results were noted in sixty-four patients, all of whom obtained relief from all symptoms of sneezing, rhinorrhea, or pruritus of the nose, palate, or eyes. Of these, fifty-nine were maintained on 2 mg four times daily; two patients took 4 mg doses; one child took 1 mg four times daily.

Moderately good results were noted in eighteen patients. Their symptoms were 75 per cent relieved, conjunctivitis cleared completely, rhinorrhea lessened, and sneezing became less frequent.

Fair to poor results were noted in ten patients. In these, the drug did

*Brand of Diphenylpyraline, Schenley Laboratories.
**Brand of Diphenhydramine Hydrochloride, Parke Davis & Co.

not give consequential relief in dosage ranges up to 4 mg every three to four hours.

Symptoms due to other than vasomotor rhinitis were relieved in four cases. One urticaria case had complete relief, and three eczema cases had the sensation of itching relieved while on the drug.

### OBJECTIVE FINDINGS

In the patients who obtained moderate to complete improvement, the conjunctivitis was completely relieved, and the nasal mucosa on repeated examination showed loss of edema and return to normal color.

### SIDE REACTIONS

Side reactions were noted in seven patients, as follows:

1. Excessive dryness of the nose occurred in two elderly women at the 2 mg dosage level. The symptom disappeared at the 1 mg level, but relief from allergic symptoms was still obtained.
2. Headaches occurred in two women, severe enough to warrant stopping the drug. Headaches cleared within four hours after the last dose.
3. Mental depression occurred in one woman on a schedule of 2 mg every four hours. With discontinuance of the drug, depression was alleviated.
4. Generalized flushing of the skin occurred in one male, severe enough to halt use of the drug.
5. Asthma occurred in one woman. All other antihistaminic drugs used on this patient had had the same effect, therefore, it was discontinued.

### CONCLUSIONS

A new antihistaminic drug, Diafen, an excellent adjunct, is valuable in vasomotor rhinitis due to pollenosis.

Excellent to good results, with moderate to complete relief from symptoms, were obtained in eighty-two out of ninety-two patients on whom it was used. Fair to poor results were obtained in only ten patients. Side reactions were noted in seven patients in whom only five suffered reactions severe enough to halt use of the drug.

One patient who had severe urticaria associated with the vasomotor rhinitis experienced complete relief on a dosage of 2 mg every four hours. Three children with eczema and vasomotor rhinitis experienced cessation of pruritus and tendency to scratch.

The incidence of severe side reactions with the use of this drug is much lower than that seen with the use of other drugs in the class of the benzhydryl antihistaminic agents, and it is equally efficacious. Only five patients were intolerant to the drug. No patient complained of sleepiness or gastric distress with any dosage level of the drug which was used in this study.

*98 S. Munn Avenue*
*Submitted February 6, 1956; Resubmitted January 9, 1957.*

# Progress in Allergy

## BRONCHIAL ASTHMA VI

### Critical Review of Literature

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WE ARE again attempting to review the literature on bronchial asthma and related conditions, this time to include a critical inspection of articles published from early 1955 to the end of 1956. In addition, we have commented on a few articles written in 1954 which were not available for Gottlieb's last excellent review on asthma, published in 1955.[1] Our own previous reviews were published in 1943, 1944, 1945, 1947 and 1949.[2-6]

Many other reviews have been published, most of them very informative. One has been written by Kaplan, Ehrlich and Aaronson,[7] with special reference to hay fever and pollen asthma. Others have come from Halpin[8] who discusses various papers, including some on asthma; and Hansen[9] from Germany, who gave a presidential address on the clinical, pathological and etiological problems of bronchial asthma and the natural history of the disease.

Education in allergic diseases is being emphasized and has had a real boost by the formation and growing strength of the American Foundation For Allergic Diseases. This organization is rapidly taking its place alongside other national groups which are battling poliomyelitis, cancer, heart disease, etc. Aided by increasing funds, the Foundation is instructing the laity and the medical profession in the field of allergy and is now engaging in research problems. Chapters have already been started in several cities. It also has granted quarterly or part-time stipends at $500.00 each for medical students in clinical allergy and the basic sciences relating to allergy.[10] These fellowships should increase the quality and number of young allergists.

Education has also been stressed in three articles by Feinberg.[11,12,13] They point out that "Allergic manifestations are many, affect millions of people, and result in extreme economic loss and disability. In the last fifty years much progress has been made in our knowledge of allergy, which makes it possible to diagnose and treat satisfactorily a large percentage of sufferers. Perhaps the greatest obstacle to maximum benefits of the care of these millions is the inadequate background in allergy possessed by many practitioners because of the meager teaching of allergy in medical schools. Imperfections in our knowledge of allergy and its more adequate management will be remedied by the increasing trend in research and the recent participation of national organizations that aim to support it." Feinberg also points out that there are only about 1,500 physicians in the United States who specialize in allergy, which means about 10,000 allergic patients to each specialist. This would be an impossible

This Review is to appear in three sections, of which this is the first.

load for the specialist; most of these patients must therefore be handled by pediatricians, internists, and by general practitioners, and these physicians are the ones who must be more intensively trained in the field of allergy.

The last two years have been notable for important advances in the use of the steroid drugs, especially prednisone and prednisolone. The literature on just these two has been so tremendous that we cannot cover it in its entirety. We can only discuss the more important articles.

Knowledge of allergy is spreading over much of the world; unfortunately, even the fundamentals of skin testing are still unavailable or poorly done in many countries, e.g. much of Asia, Northern and Middle Africa, and many islands. Good doctors from these places should be trained in allergy and should return to their countries so that they can help the allergic sufferer. Both of us have traveled widely and have never been in any place where asthma and other allergic diseases were not present.

Much new knowledge, too, has come in the field of pulmonary function tests. The time has now come when every allergist should have some sort of apparatus in his office by means of which he can, from time to time, test the breathing capacities of his patients. Improvement as shown by these tests constitutes a major psychological aid in therapy; the machines demonstrate the increase in breathing ability, and the patients take on new vigor and vitality. In addition, the use of these machines is valuable in testing efficiency of new and old drugs.

From the historical point of view come three recently published papers. Maimonides,[14] who treated Saladin's minister for asthma and who also wrote his "Treatise on Asthma" about 1190, told physicians to be both practical and theroretic. He urged the use of expectorants and cautioned doctors to keep the asthmatic lungs moist. Tull, in 1889, obtained excellent results in severe asthma by giving 30 drops of the fluid extract of Euphorbia Pilulifera in a wineglass of water every three hours,—this "to be used conscientiously and persistently, with proper intermissions, for a long period of time, in many instances for two years or longer." Unfortunately, the author and others also gave a great deal of morphine sulfate in ¼ grain doses.[15] [It must be remembered that in those days morphine was about the only potent drug available for asthmatic patients. Adrenalin and aminophylline had not yet been discovered, and ephedrine was not used in the western world.] Mescaline[16] played an essential part in the lives of the American Indians before the white man came. It is the most active alkaloid of a small spineless cactus *(Lophophora williamsii),* and its formula is strikingly similar to that of adrenalin. Its use leads to hallucinations, and similar symptoms can apparently come from injections of old pink adrenalin which has in it a substance called adrenochrome, closely related to adrenalin and to mescaline.

## NEW BOOKS

Glaser's "Allergy in Childhood" is an outstanding publication. It is very readable, the illustrations excellent, the contents interesting. It is especially recommended for the pediatric allergist but every physician can learn something from its contents. Minor objections exist as in most books: immunologic information may be a bit scanty, and even the suggestion regarding limited use of Demerol® in status asthmaticus should have been omitted.[17]

Barach and Bickerman[18] have a fine book, with chapters by sixteen other men. This volume deals with the medical management of pulmonary emphysema, as it is carried out in their clinics at Presbyterian Hospital (New York). It discusses at length the various problems of emphysema and its pathogenesis, physiology, varieties, and its treatment by breathing exercises, oxygen, bronchial drainage, care of infections and complications, e.g. cor pulmonale. Included is an excellent chapter on respiratory function tests. This large book has one major drawback in that it does not give enough attention to bronchial asthma which is the major cause of one of the important varieties of pulmonary emphysema. That fact should be stressed and emphasis should be placed on search for responsible allergens. If asthma is prevented or diminished the number of emphysematous patients will decrease. We ourselves have noted that, as our knowledge of allergy and as education of the public have increased, we see less and less emphysema, especially in children and young adults.

Samter and Durham and thirty-seven co-workers[19] have a very informative volume on "Regional Allergy of the United States, Canada, Mexico and Cuba." Each contributor has written a short survey of his respective area, and has evaluated the geographical, social, climatological, botanical, and environmental factors that are pertinent to his particular region as they affect allergic patients. There are valuable data on pollen and mold spores, pollen incidence, etc. In this single volume, for the first time, can be found a comprehensive, more or less complete and practical study of local allergic problems.

In Kallos' "Progress in Allergy IV" is a chapter on experimental asthma by the Noelpps. There are three chapters which deal with the adrenal steroids. Maunsell has a fine chapter on respiratory allergy to fungus spores; this includes the classification, identification, diagnosis, testing, therapy, and culturing of molds. Kallos himself gives an excellent review of current progress in allergy.[20]

Taub[21] has a second edition of his "Clinical Allergy," 11 years after the first. The book is small but good for the general practitioner. "Asthma Bronchiale," by Wys of Stuttgart is in German.[22]

In Fishbein's 1955 and 1956 Medical Progress are excellent chapters on allergy written by Waldbott[23] and by G. T. Brown,[24] respectively. The latter book has in it a useful list of the trade and generic names of antihistaminic drugs. In Current Therapy, likewise for 1955 and 1956, are good sections on various allergic conditions, including asthma.[25,26]

Miller and Baruch have a new book entitled "The Practices of Psychosomatic Medicine as Illustrated in Allergy."[27] The authors are to be congratulated as regards their approach in handling children. One reviewer objected on the grounds that the book was "too sexy" and too positive.

Other books have appeared in the past two years:

"Allergy Cooking: A Guide with Menus and Recipes,"[28] a book with over 600 easy-to-prepare recipes and menus suitable for diets that must exclude milk, egg, wheat, cereals, etc.; an excellent supplement to proper medical therapy.

"Clinical Physiology of the Lungs," by Drinker, with a wealth of concrete facts about breathing.[29]

"Diseases of the Chest," by Hinshaw and Garland,[30] with a concise discussion of pulmonary function tests, allergic pulmonary conditions, et cetera.

"Principles of Bacteriology and Immunity," by Wilson and Miles,[31] in two volumes.

"Antibiotics and Antibiotic Therapy," by Hussar and Holley,[32] with much reference to penicillin reactions.

"Immunity," by Hideo Moriyama.[33]

"Allergy and Asthma. The Relationship Between Allergy and the Autonomic Nervous System, Especially the Parasympathicus." The two Takinos remind us that disturbances of the autonomic nervous system should be included in our thinking, and they believe that increased tension of the parasympathicus (greater vagus system) can explain the symptoms.[34]

Kämmerer and Michel have a large book, in German, on Allergic diatheses and diseases.[35]

### IMMUNOLOGY AND PATHOGENESIS

The "Seminar on Allergy"[36] is a classic and should be read in its entirety by everyone interested in the field of allergy. There is a foreword by Gutman; an article on "The Genesis of Antibodies" by Harris and Harris; on "Types and Distribution of Antibodies" by Kuhns; on "The Delayed Type of Allergic Inflammatory Response" by Lawrence; on "Diagnostic Methods for Allergic Disease" by Sherman; on "Bronchial Asthma" by Lowell; and on "Life Stress and Allergy" by Wolf.

This volume contains ninety-three pages which are full of authoritative, interesting, and up-to-date information. The article by Lowell is especially good. He discusses terminology, and then points out that "the pathogenesis of asthma and emphysema (the so-called obstructive pulmonary irreversible type) has important similarities and clinically the features of the two conditions overlap so strikingly as to make it impossible to draw a line between them. Most of the studies on obstructive disease have been made in emphysema. However, all the abnormalities of ventilation which have been described in emphysema are also demonstrable in asthma." Lowell then discusses factors which affect resistance to the airflow in the bronchial tree. Patency depends on (a) the degree of expansion or collapse of the lung; (b) narrowing of the airway by contraction of smooth muscle or by fibrosis in the wall of the bronchial tree; and (c) encroachment on the airway arising from swelling or thickening of the bronchial walls by edema or inflammation. We heartily agree with Lowell when he states that "At present, there is no direct evidence in man for bronchospasm as the cause of, or the principle factor in, the development of an asthmatic attack. For this reason the words 'bronchospasm' and 'bronchoconstriction' should not be used synonymously with obstruction." [We add that the words "bronchospasm" and "bronchial asthma" likewise are not interchangeable.]

Lowell then discusses pulmonary function in asthma, the induced asthmatic attack, the relationship between allergy and asthma, the use of ACTH and the adrenal steroids, and some therapeutic implications.

*Electrophoresis* and its relationship to bronchial asthma and other bronchial diseases has been discussed by several authors, including the long article by Harris and Harris in the above-mentioned report.

Tuft,[37] from the Jewish National Home For Asthmatic Children in Denver, found that serum paper electrophoresis, in 121 asthmatic children, revealed lowered albumin and elevated alpha two and gamma globulin. Those children who were asthma-free for at least thirty-one days showed only the albumin and gamma globulin changes. Steroids

affect the electrophoretic pattern by increasing albumin, increasing alpha 1 globulin, have no effect on previously elevated alpha 2 globulin, and decrease gamma globulin levels toward normal. He found thirteen cases with an unusual electrophoretic fraction in the alpha 2-beta area, but not one of these 121 children exhibited agammaglobulinemia, despite the fact that the history in all cases revealed a distinct susceptibility to repeated respiratory infections.

Tuft further states that "since gamma globulin was found to be present in at least normal amounts in all cases, the parenteral administration of this agent on quantitative grounds alone would seem unnecessary. However, hypergammaglobulinemia was demonstrated in (his) group C, the group studied at least thirty-one days after asthma. Increased amounts of gamma globulin at least accompany the recovery phase. One may postulate that such increases are necessary for recovery and thus provide a basis for injection of this protein. Proof of the postulate may serve to substantiate the excellent clinical results of Bowen[38] with injected gamma globulin in a group of seventy-five patients with winter asthma."

Ferri et al[39] studied the sera of forty-four asthmatic patients by paper electrophoresis. In nine of the forty-four samples it was possible to see, perfectly differentiated, an abnormal component migrating between the beta and gamma globulins. In some cases this component was not seen; in others, it was not possible to separate it from the beta globulin.

Agammaglobulinemia has been studied. Good[40] feels that his observations support the concept that plasma cells are directly involved in the sequence of events resulting in the formation of antibodies and gamma globulin and the liberation of these proteins into the circulating blood. Good and Mazzitello[41] also discuss the infectious pulmonary diseases which are apt to occur in patients with agammaglobulinemia.

Capuani[42] had previously shown a decreased fibrinogen content of plasma proteins in the patients with bronchial asthma. He adds that the electrophoretic pattern shows very slight but constant modifications of plasma protein fractions, consisting of a moderate tendency to hypoalbuminemia and beta globulinemia, and an equally moderate tendency to an increase of gamma globulin. Benda and Urquia[43] think that serum electrophoretic studies in asthma may be of help qualitatively, not quantitatively. Among other workers in this field are Hayles et al,[44] and Young and his associates.[45]

Bram Rose[46] comments: "Of no therapeutic or diagnostic aid at present, but nevertheless of great interest, are the alterations in the plasma proteins and the location of reagin or skin-sensitizing antibody. Changes in the globulin similar to those observed in the collagen diseases, although much less marked, can be demonstrated in the plasma proteins of many asthmatic patients. These consist of moderate increases in the beta and gamma globulins. It is surprising, therefore, to find that reagin or skin-sensitizing antibody is almost wholly confined to gamma globulin."

This type of research is new and interesting, but much more work is necessary before we can draw any definite conclusions as regards the relationship of electrophoresis to bronchial asthma and other allergic diseases. One of the major unsolved problems is the significance of the qualitative observations and their relation to quantitative changes which at present we seem to have no true way of measuring. Perhaps the newer work on gel diffusion may help.

*Histamine, acetylcholine,* etc.: among many articles relating to the role of histamine as a cause of attacks of asthma is one by Halpern and

co-workers,[47] who showed that trauma to guinea pigs increased their susceptibility to shock from histamine and also to such allergens as egg albumin.

In an excellent review of the pharmacology and functions of mast cells, Riley[48] states that these cells contain both heparin and histamine. Eosinophiles have been shown to have antihistaminic properties, and are probably more concerned with the detoxification and disposal of histamine than with its elaboration. Benda et al[49] injected guinea pigs with blood serum from sixty-eight patients with asthma and serum from another thirty-two patients with chronic bronchitis plus wheezing. In sixty-four of this combined group this serum did not protect guinea pigs exposed to histamine aerosols; in the other thirty-six relative protection occurred. Then these 100 patients were given injections of blood serums from normal persons, with or without the addition of prednisone. After this procedure the serums of these patients were again injected into guinea pigs and the animals were again exposed to histamine aerosols. The serums of fifty-nine patients who were benefited clinically did provide increased protection to the guinea pigs. The serums of twenty patients who were not benefited did not change the reaction of the animals to the histamine aerosols. The results of the "protective tests" in the guinea pigs thus were consistent with the therapeutic results in seventy-nine patients. While these results were fairly good a number of inconsistencies occurred.

Ratner[50] has a nice discussion on allergy and anaphylaxis. He concludes "Allergy is the battle against the invasion into the body of foreign substances and may ensue when the organism fails to prevent the entrance of inimical agents into the circulation. The major role of allergy is played by the antigen-antibody tissue reaction which results in physiologic disturbances in the affected tissue and subsequent spasm of the involuntary smooth muscle." [Is this concept correct? Edema in muscles and other tissues is probably more important than spasm.]

Ratner said "that wheal formation, the ultimate unit of the allergic reaction, is the result of an arteriolar spasm mechanism which is the basis of all allergic vascular reactions. Other mechanisms may play minor roles in the allergic reaction but the type of syndrome evoked depends on the strategic location of the smooth muscle affected by the antigen-antibody reaction." Ratner also states that histamine does not play a major role in the resultant physiopathology of allergic reactions, but, if anything, a very minor role. Though many tissues are affected, the major reaction, that in the bronchi, dominates and overshadows all others. Edema is secondary to muscle spasm.

Salazar Mallen (Mexico City)[51] also discusses the physiopathology of bronchial asthma, especially the different mechanisms responsible which lead to liberation of musculo-active and vasculo-active substances which in turn cause spasm and edema. He states that chronic hypoxia due to bronchial asthma leads to increased cardiac activity and pulmonary hypertension and these then cause chronic cor pulmonale. [This theory should not go unchallenged. We, among others, believe that *uncomplicated* bronchial asthma, no matter how severe, is a very rare cause of either right or left heart failure. In our experience those who finally show left heart failure have some other cause, e.g. hypertension or coronary occlusion. Those who develop cor pulmonale have some such associated pulmonary condition as severe bronchiectasis, pulmonary fibrosis, tuberculosis, or silicosis, or kyphoscoliosis.]

Van Geuns[52] realizes the difficulties in assessing the various theories as to the cause of asthma. He feels that the allergic constitution is the primary factor, but this can become operative when infectious, social or psychic factors occur.

Benaim et al[53] showed that injections of sodium nucleate in guinea pigs lessened asthma induced by antigen aerosols; bilateral adrenalectomy did not increase sensitivity. Panzani[54] found that inhalation of 1 per cent aerosol acetylcholine for one to three minutes had no effect on normal individuals, but, in asthmatic patients, it led to distinct reductions in vital capacity, pulmonary capacity available on effort, and maximum utilizable volume. This test was also usually positive in naso-sinusal allergy, spasmodic cough equivalent to asthma, and allergic bronchial catarrh in children and young adults. The test, however, was negative in infectious conditions of the tracheobronchial tree.

Bram Rose[46] points out that despite many studies the exact mechanism of allergy is still unknown. "Susceptibility to the effects of histamine or acetylcholine is prone to occur. Thus neither substance will induce bronchospasm unless the patient is asthmatic. Histamine metabolism itself is altered, with considerable fluctuations from the normal in blood and tissues as well as impairment of several mechanisms for the inactivation of histamine. Undoubtedly, other metabolites with the capacity for smooth-muscle contraction and mucous-secretion stimulation are involved in the production of asthma, but are not known at present. It is a bad principle to invoke a multiplicity of causes for a single disease; yet one is forced to assume that probably only some cases of asthma are due in part to histamine release; and these, usually in children, respond to adequate antihistamine therapy."

Michelson and Lowell[55] compared twenty-eight asthmatic patients (twenty men, eight women), with twenty-eight normal individuals. In 231 blood samples from both groups, they found no activity characteristic of acetylcholine in the whole blood, plasma, or serum. Tiffeneau[56] showed that the lungs of asthmatics are extraordinarily sensitive to histamine and acetylcholine, whereas these same drugs have little effect in normal persons. There is a close correlation between the degree of sensitivity to acetylcholine and the stage of development of asthma, but hypersensitivity to this drug is demonstrable even before the first attack of asthma. Acetylcholine acts on the pulmonary smooth muscles, the function of which is regulated by both the sympathetic and parasympathetic systems.

Von Scherrer et al[57] did extensive studies on eight asthmatic patients (ages twenty to thirty-four), in whom attacks were induced by inhalations of allergens or 3 per cent histamine. They conclude that an asthmatic attack constitutes an acute bronchial obstruction. Its pathophysiology reflects a complex mechanism of adaptation. At first there was an increase of the functional residual capacity leading to an economical repartition of the increased work of breathing against elastic forces and against viscous forces of the lungs. The dynamic compliance of the lungs was markedly reduced in all cases. The viscous resistances were increased, but less than expected. The elastic as well as the viscous work of breathing during asthma averaged five times greater than before the attack was provoked. Hypoxemia was usually present, but hypercapnia (respiratory acidosis) was rare.

The functions of histamine were discussed in London.[58] Antihistaminic drugs have usually been unsuccessful in the treatment of asthma; his-

tamine is probably not so important in anaphylaxis and allergy as was formerly supposed.

The role of serotonin is now being studied in its relation to histamine, anaphylaxis, etc. These studies should be helpful.

Swineford[59] has a general outline of immunology. He is attempting to find out if desensitization with haptens (which neutralize antibodies but do not elicit them) will be more lasting and therefore more desirable than desensitization with whole antigens.

### PHYSIOLOGY AND PULMONARY FUNCTION TESTS

Farber and Wilson[60] stress the necessity for clinical studies in connection with pulmonary function tests. These should be as simple as possible for the average medical student and practitioner, with extensions for more involved studies when necessary, e.g. gradients for oxygen or venous admixtures. Students should be trained to think of pulmonary physiology as an integral part of clinical medicine. Students at the University of California School of Medicine are expected to master the basic principles of pulmonary physiology during their general training in physiology and cardiology. Clinical application is stressed. Pulmonary function studies are demonstrated, and the students are encouraged to act as "guinea pigs" to see how the tests work. A useful apparatus is no longer too expensive. Some kind of low-resistance spirometer, gas meter, Douglas bag, and appropriate valves and connections can provide all the basic information usually required.

To Levine,[61] the respiratory unit, consisting of many separate interrelated parts, must be considered as an adaptive and compensatory mechanism for an understanding of normal and impaired function. Until changes are far advanced disease may exist without symptoms. Such diseases cause relative to complete disability, and this slow progression explains the comparatively short history in many patients with chronic pulmonary disease. Real improvement, Levine continues, comes only after prolonged treatment with mechanical and pharmocologic aids, restoring the function of inactive lung areas and alveolar capillaries.

The *anatomy* of the lungs has been studied. Beautiful bronchograms and diagrams (in color) showing bronchopulmonary segments have been prepared by Lehman and Crellin.[62] These diagrams provide a convenient reference to the distribution and nomenclature of segmental bronchi. Pulmonary innervation and respiratory function have been described by Salek and Sendelar,[63] and by Krahl,[64] in a long article on the finer structure of the lung.

*Pulmonary function tests* have become more and more important and many articles have appeared. Probably the most elaborate are those of Gaensler,[65] which appeared in three sections, along with a lengthy bibliography. [The reader is urged to read all three in full.] It is a review of clinical pulmonary physiology, with sections on classification, ventilatory insufficiency, spirometry, lung volume, vital capacity, inspiratory capacity, expiratory reserve volume, and many other related subjects.

Motley[66] agrees with Levine: "Because of man's large pulmonary reserve, severe functional respiratory impairment may be obscured. Obvious symptoms of conditions such as pulmonary fibrosis and emphysema appear late, at which time proper treatment becomes more difficult."

Motley[67] also states that an accurate evaluation of pulmonary function impairment may be made from the following physiologic tests:

1. Ventilation measurements from spirogram tracings (total and three-second vital capacities, maximum breathing capacity, and the shape of the exhalation curve following a deep breath).
2. The degree of bronchospasm present.
3. The residual air capacity or alveolar nitrogen per cent after seven minutes of oxygen breathing.
4. The arterial blood oxygen saturation at rest and immediately after step-up exercise.
5. Oxygen uptake during step-up exercise.
6. Percentage oxygen extracted from the inspired air.
7. Character and duration of dyspnea after step-up exercise.

Many articles concern the physio-pathology of the lungs, with special reference to asthma. Colldahl[68] found that in severe asthma the pulmonary ventilation and oxygen uptake are lower, but in mild asthma these may rise above normal. Severe chronic asthma usually causes a fall of body temperature, while mild persistent asthma brings on a rise,—therefore the rise in body temperature is not necessarily due to complicating infection. Systolic and diastolic blood pressure usually increase markedly in severe attacks [it must be remembered that ephedrine, epinephrine and the steroids given for asthma may themselves cause hypertension].

Franklin et al[69] found tracings made on a rapidly moving kymograph during performance of vital capacity tests are valuable measures of pulmonary function. Normal adults expelled a volume 70 to 85 per cent of the vital capacity in the first second; children more than 85 per cent; elderly subjects with no evident pulmonary disease as little as 70 per cent. In the absence of pulmonary disease, no change in rate of expiration or vital capacity was noted after a bronchodilator drug. Marked changes in the tracings were found in different pulmonary diseases, e.g. bronchial asthma, pulmonary fibrosis and sarcoidosis. In most cases the expirogram proved a better guide to therapy and to the course of the disease than did x-rays, or clinical or subjective improvement.

Roy, Chapin and Favre[70] measured the mean velocity of forced maximal expiratory and inspiratory air flow in forty normal subjects, thirty symptom-free asthmatics, and twenty-nine patients with active asthma. Tests were made before and approximately fifteen minutes after injections of epinephrine. Comparison of results in these three groups emphasized the equal importance of both volume and time of expiration in the evaluation of respiratory efficiency of the asthmatics. The mean velocity of forced maximal expiration was the most sensitive test of ventilatory efficiency; the vital capacity was the least sensitive; the first one-second capacity was rated between the two. The mean velocity of forced maximal expiration was especially accurate in patients over forty, as compared with lower age groups.

Guerrant[71] has a good paper on abnormal physiology in asthma. Structural changes with allergic asthma consist of edema of the bronchial mucosa, hyperactive mucous glands, and spasm and hypertrophy of bronchial muscle. If infection is also present the edema becomes inflammatory and bronchial secretions become purulent. With chronic asthma alveoli become distended. Over-distention of pulmonary vessels with stiffening of the lung may cause many symptoms of asthma. Physiologic changes in asthma include overdistended lung; reduced vital capacity, rate of air flow, and breathing capacity; poor intrapulmonary mixing; increased intrathoracic pressure; increased or decreased minute ventilation; reduced

oxygen uptake and arterial oxygen saturation; and increased arterial carbon dioxide content.

The etiologic foundations of dyspnea have been divided by Overman[72] into (1) ventilatory (asthma belongs in this group), (2) respiratory, (3) circulatory, and (4) psychogenic. The various factors are well discussed. Comroe[73] has an informative circular on dyspnea. He states "There is an amazing lack of precise information regarding the origin of one of the commonest symptoms encountered in clinical practice. Theories of the genesis of dyspnea should be supported or disproved by more direct experimentation. One might also predict that in the great majority of patients with dyspnea, the physiologist will be able to identify and quantify alterations in the mechanical factors in breathing, and that more widespread use of the newer tests of pulmonary function will bring in most patients with cardiopulmonary disease and disability."

## ETIOLOGY

### A. *Constitutional Factors (Inheritance)*

In discussing the role of heredity in asthma Susan Dees[74] states the history many times is inadequate insofar as the allergic child from the non-allergic family is concerned, when compared with allergic families, and in many cases the information is therefore biased. Her feeling is that insofar as the "close" family relatives are concerned the incidence of allergy is small, but for "distant" relatives there is about 55 per cent incidence. [Our personal experience suggests much higher rates for both "close" and "distant" relatives.]

Sugihara,[75] in his study of 5,026 asthmatic patients found the following rates: only father had asthma, 28 per cent; only mother, 32.4 per cent; both parents, 12.2 per cent; paternal grandfather, 23.1 per cent; paternal grandmother, 23.2 per cent; only maternal grandfather, 27.1 per cent; only maternal grandmother, 21.1 per cent; both paternal grandparents 14.3 per cent; and both maternal grandparents, 30.8 per cent.

Sutherland[76] (Australia) believes only those individuals with a particular constitutional make-up or diathesis are capable of developing real asthma and the essence of this diathesis appears to be an undue responsiveness to trivial stimuli.

Wittich[77] states "it is well known that when both parents have definite allergies the incidence of a major allergy is increased as a result of this bilateral inheritance, and that a child of such inheritance is more refractory to proper antiallergic management." If a husband and wife both have major allergies "their offspring should receive adequate tests before allergic symptoms develop to determine whether they will become allergic, and measures of elimination including attention to foods and environmental factors, to prevent clinical symptoms should be undertaken. This type of prevention has been very successful." [As far as we know, there are no tests to tell whether or not a child will become clinically allergic. But we urge that steps be taken in all children of allergic parents so that exposure to known potent allergens should be minimized.]

Eriksson-Lihr,[78] in a study in Western Finland of 4,832 public school children, found 328 (6.8 per cent) were allergic and 0.6 per cent had bronchial asthma; in Helsinki, of 27,999 school children, 1019 (3.6 per cent) were allergic. Asthma was more frequent in boys. Vallery-Radot et al,[79] in a study of 803 cases of asthma, found 53 per cent where

of allergic origin; 34.3 per cent of bronchitic origin; and 5 per cent were due to diseases of the respiratory, endocrine, vagosympathetic or digestive systems. In 7.7 per cent the etiology was uncertain. Allergic asthma predominated in children. There were 427 cases of allergic asthma in which the diagnosis was based on cutaneous and intradermal tests, eosinophil counts in the blood and saliva, and x-ray studies of the thorax. [We prefer to base the allergic criterion on the history and physical findings, using the laboratory work for supplemental confirmation.]

### B. *Specific Factors*

*Inhalation.*—The above authors[78,79] state that, in their 427 cases of allergic asthma, "the most frequent cause was *house dust* (55 per cent). Of 238 cases, in which there were positive skin tests to dust, forty (17 per cent) were due to dust only, 109 (46 per cent) to feathers and dust, and twenty-four (10 per cent) to hair and dust. Sixty-five (27 per cent) were due to all three."

Targow[80] emphasizes, with examples, that clinical house dust sensitivity is possible at any time of the year, and that the time of occurrence and length (if seemingly seasonal) may vary in different patients but is constant for any one patient. He theorizes that the apparent seasonal nature of dust sensitivity may depend on the "catalytic" effect of meteorological factors such as temperature or humidity to which individuals may differ as to their reaction. But his major contribution is to point out that it may be the combination of the pollen plus house dust that results in symptoms, when pollen hyposensitization alone is unsuccessful, at which time clinical dust sensitivity must be kept in mind. [We frequently find that some people must avoid certain foods during specific pollen seasons, and therefore we do complete skin tests in all patients with respiratory allergy.]

Van Geuns[81] indicates many patients give positive tests to house dust extract but not to the materials which make up house dust. Therefore house dust has a specific allergenic effect. He thinks the house dust in all countries possesses the same allergenic effect, although the exact nature of house-dust-antigen is still unknown even after studies by electrophoresis and ultrafiltration. This antigen consists of big molecules resembling chemically carbohydrates, or aminosaccharides, and, curiously enough, cocci capsules. Previous workers have shown that excessive humidity increases house dust allergy, probably through mold action. Schuppli,[82] in 900 asthmatics, believes that up to age 25, asthma is mainly caused by an allergen which is contained in the dust from the patient's own bed. While the nature of this allergen is not clear, it is missing in the mountains district. Van Geuns[81] found the house dust from the lowland (i.e., Holland) has a stronger allergenic effect than the house dust from the high mountains (i.e., Davos, Switzerland).

Fior and Teseo[83] speculate on whether humidity renders house dust more allergenic, and whether fungi produce breakdown products from organic material such as paper, wool, feathers, and other substances, which contribute to house dust allergenicity. [The factor in house dust is still an enigma. We are fortunate that good house dust extracts give positive scratch and intradermal reactions and are also effective in hyposensitization.]

Glaser[17] states that most cases of perennial bronchial asthma appear to be caused by pollen sensitivity, especially to ragweed. Wodehouse[84] from his gel diffusion work says that short ragweed produces at least

eight antigens. These findings coincide with results with chemical fractionation, electrophoresis, and chromatography of ragweed and other pollens. Autoclaving destroys all antigenic activity. [There is much other work published and still going on by means of gel diffusion, chromatography, and electrophoresis in the hunt for the substance in these pollens, which is *"the"* specific cause of the allergic response.] By recording the fluctuation in ragweed pollen concentration throughout twenty-four hour cycles, Gurney and Cryst[85] found a pattern of higher ragweed pollen concentration at mid-day and lower concentrations in the late evening and early morning hours, with some exceptions. The symptoms of patients studied do not correlate readily with ragweed concentration (symptoms more prominent in the morning and decreased at midday) but suggest an interesting independent pattern. [That is, if one believes the allergic response must be prompt.]

Harkavy[86] has re-listed in order of importance the tree pollens (elm, maple, poplar, oak, birch, sycamore, and hickory), pointing out oak is most widespread; alder, hazel, and pecan are less significant except in Georgia and northern Florida; cedar plays an important role in Texas and Bermuda; and in Washington, D. C., the paper mulberry is a potent cause of spring hay fever. Also regionally important are the Mesquite Tree in Texas, black walnut in the Sacramento Valley, and the olive tree in California. Evergreen such as pine, spruce, balsam and hemlock affect but a small group of sensitive individuals. [This is an excellent and detailed paper with "meat" in every sentence. In twelve pages he covers much in the field of allergy. Since it is only published in a surgical journal we can only hope that it is read by many and that readers appreciate his effort.]

The British Association of Allergists published an interesting series of papers[87] on the problems of aerobiology. Gregory believes that like pollens (trees, grasses, weeds), the principal sources of fungus spores composing the air-spora are situated above soil level: (a) dead or moribund vegetation; (b) leaves and stems of living plants bearing epiphytic yeast colonies or attacked by pathogenic fungi; and (c) mushrooms, toadstools and bracket fungi. They do not know whether all constituents of the air-spora are potential respiratory allergens. Hamilton found all molds (except penicillium) fewer in London than in rural districts. Frankland suspected that grass hay fever symptoms which continued at the end of the season out of all proportion to the pollen count were caused by some other factor, perhaps spores, and not infection. [We agree.] By use of diaries, Maunsell, in fifty-eight unselected asthmatics at King's College Hospital, London, determined three peaks of increased incidences and severity of asthma. First peak was mid-May and coincided with the peak of tree pollen; the second, June 20-27, corresponded with the peak for grass pollen; the third, at the end of July indicated a relation either to the occurrence of lime pollen and/or the increase of the spore concentration. [We have a spore season between the grass and ragweed seasons, and again between the end of the ragweed season and early winter. There is overlapping in both cases. In some individuals who are sensitive to both grass pollen and fungi, or ragweed or fungi we find symptoms occur during the respective pollen season not only on the days the pollen counts are high, but also on days when pollen counts are low and spore counts are high. Thus we think not only of house dust as suggested by Targow, but also fungi. If one is allergic he has the capacity to become sensitized any time. This in turn indicates that while in one year the

patient may only be ragweed sensitive, the next year he may have acquired a new sensitivity. Allergic mechanisms are dynamic and not static.]

Hyde,[88] in a three-year survey (1951-1953), at eight stations in Great Britain found the following spores to be most common: in summer, *Cladosporium (Hormodendrum),* 37.8 per cent; *Pullularia,* 10.4 per cent; *Epicoccum,* 3.4 per cent; *Botrytis,* 2.7 per cent, *Alternaria,* 1.0 per cent; and *Candida,* 1.6 per cent; in winter, *Aspergillus,* 2.9 per cent; *Oospora* 2.6 per cent; *Phoma,* 3 per cent; *Sporotrichum,* 2.1 per cent and *Penicillium,* 9.1 per cent. *Cladosporium* was much more common in rural areas, (70 to 80 per cent of total catch, as compared with 40 per cent in large towns). *Penicillium* was more abundant in cities. Of 627 asthmatic patients, fifty-two (8.5 per cent) were positive to *Cladosporium* but only twenty-six (4 per cent) were regarded as clinically sensitive to that fungus spore. All these patients had asthma occurring in the summer months coinciding with the *Cladosporium* season. Eleven of these gave no other positive tests. Two per cent of all patients had positive skin tests to *Alternaria* but only one per cent was clinically positive.

Ordman and Etter,[89] Johannesburg, South Africa, with mold plates exposed each day for three minutes at 11:00 A.M., on top of a three-story building, found the following: *Cladosporium,* 32.5 per cent; *Alternaria,* 12.3 per cent; *Penicillium,* 10.1 per cent; *Epicoccum,* 10.1 per cent; *Phoma* 8.3 per cent; *Monilia,* 6.2 per cent; *Torula,* 4.7 per cent; others about 1.5 per cent.

Evans and Ruiz,[90] using petri dish exposures in San Jose, Costa Rica, from March to August 1954, found *Cladosporium* most abundant. They also found *Penicillium* and *Aspergillus.* Cadrecha-Alvarez and Fernandez-Castro,[91] Havana, Cuba, found *Hormodendrum,* 30.2 per cent; *Aspergillus,* 19.2 per cent; yeasts, 16.2 per cent; *Penicillium,* 2.7 per cent; *Alternaria,* 0.8 per cent; and other fungi in small numbers. Mold spores in Havana have two general peaks, April through May, and October through November. A study of seasonal prevalence in 1200 cases of rhinitis and asthma showed 69 per cent occurred in winter (October-November); 7 per cent in summer (April-May); and 24 per cent non-seasonal.

Prince, Kaplan, and Morrow[92] say that *Alternaria* mycelium is about as allergenic as the spore. Morrow, et al[93] found bacteria were present "in all seasonal and dust plates and counts of the spore forming bacteria were greater in the dust plates. Seasonal counts of the non-spore forming bacteria were higher than those of the spore-forming bacteria. Actinomycetes were present in all of the seasonal and dust plates. Counts were lower than those of bacteria. Yeasts were not always found." [Previously, we believed that extracts made from mycelia were much less potent than those from spores.]

Werf[94] in an excellent four year study of 176 factories and workshops found it "advisable to adopt the concept 'association in mycology,' as suggested by Westerdijk, to define a specific combination of micro-organisms characteristic of each decaying biological substrate." A number of examples which may be of medical importance in general, and of allergic importance in particular, are given of fungus associations, occurring in workshops and factories where a considerable number of individuals with asthmatic and asthma-like symptoms were found to be employed. The majority of investigators engaged in the study of fungus allergy assume that when a patient shows hypersensitivity to fungi, this is almost invar-

iably due to the repeated inhalation of airborne mold spores. It has been established with certainty that the ingestion of fungus substances can do the same."

Leopold[95] points out that synthetic fibers (Dacron, Nylon, Dynel, and Orlon) are thought to be non-allergenic and free of dust. However, these can develop charges from static electricity when friction occurs. A magnetic action results which attracts increased quantities of dust and other particles from the air. He presents a case of a woman sensitive to dust and other allergens who developed bronchial asthma from dust accumulated on a dynel blanket and dacron pillows, with relief from her attacks when these were removed. [Interesting, but this certainly requires further clarification since one case is not conclusive.]

Feinberg et al[96] confirmed and enlarged on previous observations regarding insect allergy. Patients with seasonal asthma or other allergies not explainable by pollen or mold sensitivity often given positive skin reactions to insect allergens. Incriminated are Mayflies, Caddis flies, mushroom flies, aphids, bedbugs, locusts (grasshoppers), bees, house flies, moths, daphnia, Mexican bean weevil, beetles, sewage filter flies and mites. Silk should also be added because of positive skin tests. However, the respiratory symptoms are probably not caused by silk fabrics but by the silk pupa, and less often by the cocoon.

In 130 patients with positive skin tests to insect extracts, fifty-four (41 per cent) had bronchial asthma; 110 (85 per cent) nasal allergy; eleven (8 per cent) atopic dermatitis; and four (3 per cent) conjunctivitis. In 43 per cent of those with seasonal symptoms, insect allergy seemed to be the missing link to explain seasonal symptoms.

Frankland[97] presented additional work regarding locusts (grasshoppers) causing allergic symptoms in fifty-three patients, fourteen of whom also reacted to cockroaches. He also states there are now over thirty different insects described as causing allergies, including scab mite, yellow fever mosquito and fleas. [Further studies of insect allergies are certainly logical as well as intriguing. Epidemiological correlation might indicate that different parts of the country are better for some asthmatics for factors other than humidity, temperature, pollens or fungi.]

As regards *occupational sensitivities,* Werner[98] reported that of 1800 subjects exposed to dust from textiles of plant origin, 414 developed signs of allergic sensitivity ranging from transient and mild symptoms to severe asthma. The morbidity is comparatively small in the cotton industry, but is high in the other branches, particularly in subjects who have been engaged in this type of work for thirty years or longer. If the number of particles per milliliter of air, of a diameter below 3 microns is measured, it can be shown that the rate of sensitization of the workers increases with the density of these particles in the environmental air of the factory. [This is most interesting and important in the field of industrial allergy.]

Shilkret[99] states asthma occurs in 5 per cent of industrial workers. About 100 occupations favor the onset of asthma. Dusts, fumes, and vapors are the most frequent offenders. Ingestion (e.g. tasters of wine, coffee, and tea) is at times important. Contact dermatitis often precedes asthma in furriers and bakers. The more important causes by groups are:

Bakers: wheat, rye, buckwheat, corn flour.

Furriers: animal danders and hairs, especially rabbit; dyes, and especially paraphenylenediamine.

Beauticians: powders and rouge with rice, orris root, henna, quince seed oil, tragacanth and Karaya gum.
Hatters: rabbit hair of felts, banana oil, oxalic acid.
Bedding and furniture workers: various animal and vegetable fibers.
Warehouse workers and grocers: occupational dusts and vapors from coffee, cocoa, tea, spices and cereals.

[A more expanded list of possible occupational allergens can be found in Unger's book on bronchial asthma.[100]] Shilkret does skin tests with factory materials and advises: (a) atopic individuals should not be employed in such factories; (b) masks, improved ventilation, isolation of dusty processes, and wet work methods all help to prevent or lessen allergic diseases; (c) hyposensitization with specific offenders helps, but is only successful if avoidance is largely possible; and (d) change of occupation is often necessary.

Ordman[101] reported on an outbreak of bronchial asthma in South Africa, caused by castor bean dust from an oil processing factory. The castor oil plant is described as is the poisonous ricin, and the highly allergenic protein substance. After the oil is removed in the processing, there is an oil-cake residue containing 6 to 8 per cent oil. This cake is usually used as fertilizer. In this outbreak more than 200 persons developed asthma or rhinitis or both. The oil cake was further expressed with resultant dry, defatted, highly allergenic dust. This dust emanated from factory-contaminated atmosphere. Duer,[102] suspecting castor bean as the cause, because of its increased use in fertilizers, did a scratch test on a thirty-nine-year-old milk truck driver in San Diego, California, who had recently developed a cough at his new home. He also had wheezing when he gardened, and was much worse when his neighbors used fertilizer. The scratch test was equivocal so an intracutaneous test with a 1:40,000 extract was done. There was a tremendous and prompt anaphylactic shock with recovery only after heroic measures. Ordman[101] correctly did not do intracutaneous tests in his study. [Caution is always necessary with castor bean. But why was the scratch test only equivocal in Duer's case? It certainly should have been strongly positive, and the intradermal test should not have been necessary.]

According to Fowler[103] on printers' asthma, sensitivity to inhaled gum acacia is becoming frequent in Great Britain. In one firm, engaged largely in color printing, 19 per cent of the printers had asthma, and a further 30 per cent had slighter symptoms due to sensitization to the gum acacia in the spray fluid. The spray is thrown over each sheet, and the alcohol in the spray evaporates leaving a layer of fine powdered gum acacia which forms a barrier between successive sheets on which the color sheet is still wet. The average duration of exposure before onset of asthma is 4.8 years, but was only half as long for six printers who had a past history or family history of allergy. Dextrin is an efficient substitute, as far as is known now.

The problem of rhinitis and asthma in bakers is presented by Pestalozzi and Schnyder.[104] Of 159 bakers, forty-two showed symptoms of respiratory allergy (all had allergic rhinitis and six also had bronchial asthma). A familial tendency to respiratory allergy was observed in twelve (28 per cent) of the forty-two, while such a tendency was observed in only nine, (8 per cent) of the 117 bakers without allergic symptoms. Young

people with a familial tendency to asthma or rhinitis should be informed about their allergic predisposition before they start their training as bakers. The authors urge desensitization for incapacitated bakers.

Gilday[105] reported that a veterinarian engaged in research with white rats developed his first attack of bronchial asthma when he entered the room where the rats were stored. When tested with a 1:1 million dilution of stock rat antigen, the patient began to wheeze within thirty seconds and needed epinephrine for relief. After hyposensitization with eight weekly intradermal injections of rat antigen, he was able to resume work in the animal room without further asthma.

Of fifty-eight asthmatic children in Copenhagen with positive scratch tests to horse dander, thirty-one developed symptoms after exposure to horses, or following inhalation or nasal application of horse dander, according to Ryssing.[106] He felt there was a correlation between the degree of skin test response and the severity of symptoms. Hyposensitization in twenty-seven patients resulted in disappearance of clinical hypersensitivity in thirteen. Another report[107] states "Moreover, it is possible that continued exposure to a potent allergen such as horse dander may produce greater sensitization with other allergens despite the use of antihistamines." [Review of these articles on inhalant factors brings to mind several questions—(a) Is there any complex inhalant substance which can be guaranteed as entirely non-allergic? (b) Does everyone have an allergic threshold, but only some have a lower threshold because of an inherited predisposition? (c) Do we fail to appreciate that the asthmatic individual is allergic and is capable of becoming sensitized to most anything if sufficiently exposed, even though when seen only one factor is apparently incriminated?]

Spain[108] reminds us again that in those exquisitely sensitive to a food, the odor of that food may cause respiratory allergy. [Perhaps this point should be considered in patients with associated rhinitis and anosmia who cannot explain some of their asthmatic attacks.]

*Ingestion.*—Withers and Hale,[109] in a review of the literature on food allergy have made a tremendous contribution. By its nature, this article cannot be abstracted but should be read by everyone. There is much which relates to asthma.

According to Spain[108] foods are most important up to the age twenty, and thereafter food sensitivity lessens. Any food may cause asthma, but especially prominent as causes are egg, milk, seafood and chocolate. Foods may cause symptoms up to twelve to forty hours after ingestion, whereas inhalants usually act more promptly. [This is not always true. Foods may act rapidly.]

Chicle allergy was demonstrated in a twelve-year-old boy with atopy (atopic dermatitis, asthma rhinitis, and urticaria) by Cortes and Montiel.[110] The mother noted respiratory and dermatologic symptoms began or were aggravated by chewing chicle; caramel or gum drops. Asthma occurred in a few minutes after chewing boiled natural chicle. Skin and passive transfer tests were positive with extracts from natural chicle, as well as with chicle fruit, gutta percha and gum arabic.

Allergy to food was the cause of bronchial asthma in 1800 patients according to Farrerons.[111] He believes that when any allergenic food is excluded from the diet for at least two years, the hypersensitivity should disappear. [Farreron's statistics seem high to us. Are these 1800 "food-sensitive" patients clinically allergic to foods and proven without doubt

by a strong history or by feeding each food at least three times to each patient? Or is the diagnosis based only on skin tests, presumably intradermal? The more experience we have with intradermal food-skin-tests the more we realize how fallible they are. The only food extracts, in our experience, on which we can almost always rely are egg, celery, some of the cereals and citrus fruits, and potent allergens such as mustard, nuts, buckwheat, and fish. His other statement "that when any allergenic food is excluded from the diet for at least two years the hypersensitivity should disappear,"—that, too, is open to question. It is certainly true that cow's milk, a weak allergen, usually ceases to be an allergen as an infant grows up. But the potent allergens mentioned above usually remain potent allergens for life.]

Ratner, Crawford and Flynn[112] state that "in the first year of life, 100 per cent of the patients reacted to foods alone or in combination with other allergens. By the fifth year this was reduced to 60 per cent." Their work was done in twenty-seven infants and thirty-seven children between the ages of two and five years with asthma, eczema, hay fever, or urticaria. Seventeen (27 per cent) of the sixty-four patients gave evidence of congenital allergy (sensitization *in utero)* by positive skin tests to foods they had not previously ingested.

Chocolate was shown to be an infrequent offender. Milk sensitivities occurred in eighteen patients (28 per cent). None of these patients reacted to milk alone. Most of them reacted to the whey proteins, less than one quarter to the casein fraction. Only this latter group required milk substitutes. Thirty-one patients (48 per cent) reacted to egg proteins; thirty (46 per cent) to one or more cereal grains, but none to rice; eighteen (28 per cent) to citrus fruits; thirty-seven (58 per cent) to sea foods. No patients reacted to ragweed alone, and practically all who were sensitive to ragweed also were to pyrethrum and tobacco. No patient reacted to grass alone. In none of the patients was timothy the sole offending grass. Tree pollen was at times the only pollen sensitivity. Most of the miscellaneous inhalant sensitivities occurred with other allergies, but occasionally these inhalants were the sole offenders. Mold sensitivity never occurred alone. Infants with allergy should be skin tested early and studied comprehensively. [Most allergists do not believe in the theory of sensitization *in utero,* and we do find patients who are only sensitive to fungi.]

### SENSITIVITY TO DRUGS

Blamoutier[113] discusses eleven aspirin-sensitive asthmatic patients, with death in two who had received very small doses. Caution and inquiry are necessary. [It is our custom to give each of our drug-sensitive patients, including those allergic to aspirin, a card for their bill-folds. This states that the patient is allergic to ———— and even small amounts should be avoided. The patients are urged to show this card to any physician who is about to prescribe for them.]

Findeisen's asthmatic patient[114] was relieved by substitution of a hard rubber denture for an apparently allergenic Piacryl material. [This is interesting though a bit doubtful.]

There are many articles on *penicillin* sensitivity and anaphylactic reactions. Matheson[115] states anaphylactic reactions to penicillin may be sudden in onset and severe, and may occur even though skin tests are negative. Most constitutional reactions occur in patients with manifestations

of atopic allergy but non-allergic children may also be sensitive. Lowell[116] states the incidence of reactions to penicillin is 1 to 10 per cent. Mazzei[117] reported a patient being treated for asthma who developed an anaphylactic reaction in two seconds after the injection. He responded to treatment. Lang and Claget[118] report a case in which oral penicillin was taken; within one minute the patient began to develop numbness, tingling of the lips and swelling and progressed to coma, shock and cyanosis, with recovery. Coleman and Siegel's case[119] has been referred to several times in the literature. It concerns a penicillin-sensitive individual who received an injection of a hormone and promptly developed his "serum sickness syndrome" plus wheezing and tightness in the chest. The source of the penicillin was traced to the sterilizer water which had also been used for sterilization of syringes used for penicillin injections. They recommend separate penicillin syringes and sterilizer. [We use separate syringes for penicillin, and sterilize the syringes by autoclave. By using the broad spectrum antibiotics more frequently in addition to the separate syringes for penicillin, even though we use a fair amount of penicillin, we have been fortunate thus far. On each patient we inquire regarding penicillin sensitivity as well as for other drug sensitivities, and make a prominent note on the front of the chart for future reference, even though it be for years later. It is obvious that in treating the individual patient, skin tests are not going to be statistically reliable. If in the individual case penicillin sensitivity or anaphylaxis is feared, perhaps it would be more judicious to use another antibiotic.] Morrisset[120] reported a case of anaphylactic reaction in an individual without a history of allergy, who had received twelve injections of procaine penicillin, the last one thirty days before his near-fatal precipitating injection.

Maffei and Napolitano[121] have an interesting article on allergic reactions to penicillin in workers in charge of the antibiotics production. Asthma was found in three of 156 workers. They felt the asthma cases were of interest because of the possibility of sensitization to penicillin by inhalation. They also point out the problem which may face the doctor if he relies on the fact that such a patient never had penicillin therapy before, but does not know the nature of the patient's work. [This should certainly make one think twice about giving penicillin aerosol. Also such information may apply to other medications given both by aerosol and parenteral means e.g. trypsin and streptomycin.]

Acording to Franceschini,[122] of 613 bronchial asthmatic patients, fifty-one (8.38 per cent) showed clinical hypersensitiveness to drugs; that to acetylsalicylic acid was the most frequent (3.73 per cent). In none of the patients were the drugs the first cause of asthma but they did aggravate it.

Ethan Allan Brown[123] wrote an excellent paper on the question of reactions to mercurial diuretics. One must distinguish between reactions secondary to diuresis and allergic drug reactions.

Tetreault and Beck[124] presented a case in which asthma and anaphylactic shock with recovery occurred in a fifty-seven-year-old man after an intramuscular injection of thiamine hyrdochloride. Massone[125] had a case of bronchospasm, cyanosis and shock produced by heparin given for thrombophlebitis. Neviaser and Eisenberg[126] reported one asthmatic attack due to meprobamate. In a series of thirty complications following smallpox vaccination Lamache et al[127] of France mentioned asthma as one complication (rare).

### ASTHMA FROM INFECTION

Ericksson-Lehr[128] pointed out that while the great importance of bacterial infection has been gradually realized, not all allergists recognize bacteria and their toxins as real allergens. She said there is no definite correlation between active infection and skin reactions. Boys were apt to start with sensitivity to pure allergens; the first found cause of allergy in girls was usually infection. In the seven to fifteen-year age group 80 per cent of the boys but only 40 per cent of the girls had their symptoms of allergy primarily from contact with foods, inhalants, etc., whereas, in 60 per cent of the girls and only 20 per cent of the boys, the allergy occurred for the first time in close connection with an infection.

Studying 500 children, she observed upper respiratory infections in over 80 per cent of the cases, while infections of the lower respiratory tract amounted to about 60 per cent. In more than half of the cases, chronic infections were found in both upper and lower respiratory tracts.

Blatt[129] has two important articles on the relationship of bacteria and fungi to respiratory allergy, including asthma. His reviews and references are excellent, and he discusses various types of vaccines. As regards his own special technique he says "It is our experience that, when the leukocytes of such patients are subjected to the filtrates of various strains of bacteria, it will be found that certain strains kill the cells within seventeen hours while the cells subjected to the filtrates of other strains remain viable. Using this technnique for the identification of the products of the bacteria causing the allergy, and treating with the appropriate filtrates, properly diluted and graduated, has given us excellent results."

Blatt also quotes Spain and Fontana[130] who state that "infective asthma has several characteristics: (a) there is often a family history of clinical allergies; (b) the patients suffer frequently from acute or chronic respiratory infections; (c) asthmatic attacks are usually nonseasonal at first. worse in winter, seldom influenced by a change in environment unless there is an associated inhalant cause, and the attacks are often severe and readily progress to 'status asthmaticus.' Such severe bouts mostly occur after age of thirty-five and many patients have had sinusitis and/or bronchitis for many years."

Fontan Balestro[131] also believes infectious asthma is much more frequent than is generally realized. Dutton[132] reports that an antigen of airborne bacteria has been therapeutically effective in three patients. The dust from home vacuum cleaners is cultured and a vaccine prepared from bacteria which give positive skin tests. A desensitizing technique is used, e.g. in one case injections were started with a 1:100,000 dilution. In Fein's patient[133] with severe bronchial asthma, pseudomonas aeruginosa was discovered by means of the bronchoscope. Appropriate antibiotics chloramphenicol and then polymyxin B (Aerosporin®) brought prompt and lasting relief and the patient has remained well for at least two years. [This is an excellent paper and points out the necessity of searching for organisms in patients who have received many antibiotic drugs and who give no results from the usual allergy therapy.

[The clinical results are apparently the main proof since bacterial allergy cannot as yet be accurately shown by skin tests. Even when skin tests are positive, injections of extracts of positive bacterial strains only lead to good clinical results in a relatively small percentage of patients. Cer-

tainly, anyone with wide experience can definitely state that in his asthmatic patients he obtains far better results with careful specific therapy (avoidance of allergens, with or without hyposensitization) than he can obtain with any type of bacterial vaccine. There are brilliant exceptions to this rule; instances occur in which autogenous vaccines give excellent results.

[Infectious complications are frequent in asthma and, of course, the appropriate antibiotic is to be used promptly. Such therapy usually brings an end to severe asthma including status asthmaticus. This success by no means proves that bacteria acted as allergens and brought on the asthma. Rather we believe the bacteria or viruses acted as complicating or precipitating factors which made the original asthma that much worse].

### *C. Ancillary (Contributory) Factors: Meteorology, Air Pollution, Climate*

Another approach to the etiology of the factors involved in asthma has been by studies of the air pollution problems and meteorology. Dingle[134] points out that since atmosphere carries allergens, long term predictions indicating the expected severity of the coming pollen season, are based on consideration of seedbed and early growth conditions in conjunction with expected weather conditions. Such forecasts may be corrected as the season progresses. Certain weather events, such as thunderstorms, produce very high pollen counts for short periods of time. Certain weather sequences, covering a period of days, produce extended cumulative effects. Considering both these factors, the meteorologist with suitable botanical guidance can make reasonable, accurte day-to-day predictions of atmospheric pollen concentrations. Predictions of atmospheric pollen concentrations, available thirty-six to forty-eight hours before gravity slide counts, would make possible anticipation of the degree of exposure on the day following the forecast and facilitate planning of daily activity. These predictions would be more representative of the general pollen concentration over an area than are spot observations. [In practice is such a precise daily determination necessary? Probably the anticipation of the prevailing pollen season is more important for the understanding of satisfactory therapy.]

Ordman[135,136] points out the striking differences in climate patterns in coastal and inland towns in South Africa. The climatic conditions of significance in the sensitive patients are the combinations of atmospheric temperature and high relative humidity in a constantly narrow range during the day and throughout the year. In the coastal areas perennial respiratory allergy is due to exogenous and endogenous factors similar to those found elsewhere, and the incidence and severity are relatively great especially on the east coast. Many persons who maintain good allergic health inland may break down at the coast; symptoms in coastal area sufferers frequently become much less or cease when they move inland. Pollen and airborne fungi are not the cause in these cases. Gutman[137] comments on increase of asthma in new immigrants to Israel which has a higher humidity factor than the place from which they came (Iraq). But he also points out that in many cases the psychosociologic factor may be prominent. In one group, patients who formerly had been inmates of concentration camps were being treated. Almost all in this group had one thing in common; before their incarceration they had been chronic asthmatics. In spite of the changed living conditions they had lost their

asthma while confined. In some a recurrence of the asthma was observed after release from the concentration camp.

Spoujitche and Danilovitch report the climatic factor is important in various parts of Yugoslavia. There are more sensitized and asthmatic patients in certain industrial centers. The industrial climate increases air pollution and increases the harmful influences of the Panonic Plain which is flat and misty. The highlands are less harmful, and the Dalmation Coast is also favorable for sensitized individuals.[138]

Kotin and Folk[139] studied air pollution and its effect on health. Such a study was difficult, and they emphasized the necessary questions in trying to determine the etiologic factors. In only one of the acute episodes of air pollution, Poza Rica, 1950, was the detrimental factor determined. It was hydrogen sulfide from a recycling and sulfur recovery plant. Sulfur-bearing compounds are highly suspect in the Donora (Pennsylvania) and London episodes, although there are no data to substantiate this. In Los Angeles, a hydrocarbon of pronounced oxidizing activity is suspected. Its sulfhydryl group is the site of the oxidant effect. In the presence of this substance, eight of twenty-one amino acids were altered, including Vitamin $B_1$ and $B_6$, cholesterol, androgenic, progestational, and adrenocortical hormones One editorial[140] discusses the problem of smog. The most widely accepted theory at present is that smog results from photochemical reactions involving hydrocarbons, oxides of nitrogen, and sunshine. It has been estimated that not counting motor vehicles, about 20 per cent of the pollutants poured daily into the air comes from domestic incinerators and burning of the various fuels for heating private dwellings. The greatest problems arise in those areas where, as in Los Angeles, a natural atmospheric trap exists. Cool air moving gently from the ocean cannot pass the mountains and cannot rise through the superimposed blanket of warmer air. Under such conditions vast amounts of pollutants that would ordinarily be widely dispersed accumulate until toxic concentrations are reached. Cholak[141] and his group determined the concentrations of ozone (as an oxident) in the atmosphere at ground level in Los Angeles. The values were as high as 80 parts per 100 million during heavy smog, in contrast to the usual level of 2 to 3 parts per hundred million (pphm) under good weather conditions. The methods currently used lack specificity but some basic comparative information concerning the probable maximum concentrations of oxident can be obtained. Values were given for various cities, (from highest concentrations to lowest: Charleston, West Virginia; Ann Arbor, Michigan; Washington, D. C.; Whiting, Indiana (Chicago); Cincinnati, Ohio; St. Louis, Missouri; Detroit, Michigan; Philadelphia, Pennsylvania; Akron, Ohio; and Elizabeth, New Jersey), with ranges from 4.9 pphm to 0.9 pphm.

Scholnicov et al[142] published a long article with tables concerning 3500 asthmatic attacks registered by patients in the city of Buenos Aires during a four year period. They felt the temperature was the only important meteorological factor and that when the temperature was above the mean value of the month attacks of asthma were fewer. When the temperature went down quickly, as much as three degrees Centigrade or more, there was a pronounced increase in the number of attacks. Only quick changes seemed to influence the attack. Atmospheric pressure, humidity, rains and winds only have influence on attacks when they modify atmospheric temperature. There is not enough information regarding the effects of positive and

negatively charged ions although they believed that they had little effect on asthmatic attacks.

Huber and associates[143] reported on the so-called "Yokohama Asthma," a disease entity which is notable as severe and recurrent "asthma" in patients with no previous respiratory difficulties. [Supposedly the patients with this entity have no further difficulty when they leave the area but what actually happens is not always known. Some cases are sent to Northern Japan and if they do not do well they are then sent to Southern Japan. The next step, if no improvement, is to return them to the States. Supposedly they were cured upon return to the States but this would not be expected if these patients really had true bronchial asthma.] In any event the "Yokohama Asthma" is most common during the fall and early winter months. The initial symptom is bronchitis with subsequent dyspnea usually occurring in the early morning. Dyspnea may become severe enough to necessitate permanent evacuation from the offending area. Biologic studies indicate that allergens and inhalants of an allergic type rarely cause the disease. Skin reactions to allergic agents are negative. Air pollution by smog and such contaminants as ether soluble aerosols and dust is apparently the primary cause. [If this is not asthma, and "all that wheezes is not asthma," symptoms must be due to a chemical irritation of the respiratory tract, with enough edema and partial obstruction so that wheezing and dyspnea occur. If, however, this is allergic bronchial asthma, there is something basically missing in the history and findings.]

Dense fog during January 4 to 6, 1956, caused almost 1000 deaths in the greater London Area. Logan[144] says that mortality records show that toxic fog was relatively uncommon in the nineteenth and early twentieth centuries but has been observed three times during the last eight years. Atmospheric pollution associated with the fogs may be more toxic. [One should comment that in all of these disastrous fogs only those with respiratory disease, e.g. asthma, or with pronounced cardiovascular conditions really suffer. The mortality and the real morbidity occur practically only in those two groups. It seems obvious that increasing industrialization has led to increasing air pollution with chemicals. Only stringent precautions against exit of these chemicals can prevent an even greater series of these episodes.]

Nelson[145] also discusses the health aspects of atmospheric pollution. Initial changes include inflammation with capillary engorgement and exudation of fluid into the lung alveoli. The patient may cough and wheeze, and respiratory effort is increased. Fluid accumulation reduces the effective respiratory volume, increases the thickness through which gas exchanges must occur, and probably decreases ciliary activity, thus augmenting susceptibility to infection.

It would not be fair in the present day and age to avoid some comment on smoking. There have been enough articles on it. Fluorescence of benzene solutions of tobacco smoke decreases to 40 per cent of the initial level after one to ten days of exposure to various degrees of light, and to 10 per cent of the original level after three hours of radiation with a quartz lamp. This change indicates that 90 per cent of the fluorescence is due to unstable components which may be related to highly reactive radical-forming carcinogenic substances per the report of Druckery and Schwahl.[146] Ryan et al[147] reported that "smoker's larynx" has (1) thicker surface epithelium, due to excess keratinization and hyperplasia; (2) more round cell infiltration; and (3) slightly more edema than that of a non-

smoker. Lowell and associates[148] believe smoking is apparently the major cause of chronic obstructive pulmonary emphysema. The condition has been observed only in patients who have smoked for several years. Dyspnea first appears after the age of forty. Expirograms show pronounced slowing of expiration even after intensive treatment with bronchodilator drugs or steroids. Coughing, hyperinflation, and musical rales and wheezing are common. [The differential diagnosis between this condition and the so-called "intrinsic" asthma of the older age groups must be difficult, if they are different conditions. However, the main reason for inserting this article here is to emphasize what smoking can do without the help of a previous, or concommitant, or superimposed allergic asthmatic condition. Smoking certainly does not help; asthmatics especially are not to smoke. There are several other articles by Fishbein.[149] Phillips,[150] Oswald,[151] and Micheli[152] on smoking, with statistics and effects, which would be only redundant if reviewed, other than to say smoking does not produce any good effects. Fishbein showed that filtered micronite cigarettes reduced the incidence of cough, expectoration and throat irritation.]

We discussed the problem of infectious allergens under specific factors while here our interest is to present the information given regarding infectious disease processes. Dintenfass[153] inter-relates the role of infection and allergy nicely. Allergy and infection may be associated in any part of the respiratory tract. A vicious cycle may be established. Allergy lowers the resistance of the mucous membranes and interferes with ventilation and drainage, leading to superimposed secondary infection. The infection, in turn, adds bacterial factors to the allergic tendency. Goldman, et al[154] from Mt. Sinai Hospital, New York, conducted a study on the relationship of nasal and sinus disease to systemic disorders. The authors reported on eight-two patients in whom complete allergic and bacteriological studies were made. Among fifty-eight cases of "intrinsic" asthma, twenty-five patients had sinus infection and thirty-three were free of infection. Among twenty-four "extrinsic" cases five patients had sinus infection and nineteen were free from infection. Of twenty-nine cases with negative x-rays, nine patients had sinus infection and twenty were free from infection. Of forty-two cases with positive x-rays, twenty-four patients had sinus infection and eighteen were free of infection. They believe that sinus infection as such is not a primary cause of asthma but rather a complication superimposed upon an altered sinus infection. Bergman and associates[155] reported that in 90 per cent of patients with healthy lungs and in asthmatics with normal sedimentation rates, the lower part of the trachea and larger bronchi were sterile. In asthmatics with high sedimentation rates, bronchial infection was present especially when the polymorphonuclear cells were found in the aspirate. When eosinophils predominated, the culture media were usually sterile. The color and tenaciousness of the sputum could not be relied on to indicate whether or not infection was present. [These last three papers are very important. Infectious complications are usually present if the cough precedes the wheezing, if the cough is more troublesome than the wheezing, or if the cough and wheezing are worse in air-conditioned places. In addition, the signs of infection are usually present (increased sedimentation rate, leukocytosis, crepitant rales).]

A case was discussed in which a woman developed severe asthma unless ovulation was suppressed; continued suppression over many months was advised.[156] Ferreira[157] presented some studies on women with allergies

of hormonal etiology. Twenty-seven patients with asthma, rhinitis, urticaria, migraine, colitis, et cetera, coincidental with days of menstruation or the ovulation time, were studied with intracutaneous tests of estradiol, progesterone and gonadotrophins. When the test was positive, a hyposensitization schedule was begun with the hormone incriminated. Results were good in twenty of the twenty-seven. [Patients with increased asthma before periods usually respond to a thorough allergy evaluation and proper care. In some cases a low salt and low water intake before periods seems helpful. Hyposensitization with hormones has not been widely accepted in this country.]

In industry the asthmatic employee presents a number of problems that must be solved if he is to remain an effective worker. Weaver[158] covers the subject well. He never observed an example of true occupational asthma in a large refinery and petrochemical plant with 7,500 employees, even in the asthmatic patients. When an employee alleged aggravation of an asthmatic condition by some gas or fume, the author found it desirable to supplement the history by observation of the actual exposure, doing pulmonary function determinations before and after the exposure. However, he points out that a slightly contaminated atmosphere that may be well tolerated by normal persons may have devastating effects on an asthmatic. The inhalation of acid fumes or chlorine gas may precipitate an attack of wheezing, but such strongly irritating substances do not represent much of a problem because steps have been taken to insure their control, and the employee with asthma knows of their existence and avoids them. Halpin, in a study of a large Quaker Oats plant,[159] also had an excellent article on industrial factors. While proper equipment is necessary to minimize exposure, cleaning and maintenance is also necessary. Gas masks have to be used at times. He also points out that, in addition to the amount of exposure, there is variability in the sensitivity of the allergic individual; some are so sensitive that change of occupation is necessary; another baker may only have minimal exposure and he can continue his work; a third baker may have respiratory allergy but from pollens and molds rather than from his bakery exposure. This one needs proper therapy but not removal from his occupation. Furthermore, Halpin points out that persons who live near a grain mill but do not work there may have to move because winds can blow grain mill dust their way. Without a history of previous inhalant allergy, respiratory symptoms in mill workers are apt to occur within twelve to twenty-four months after initial *close* exposure. In those with prior pollen, mold or dust sensitivity, symptoms may occur the first day of exposure. Such workers should seek other occupations; they should never have set foot inside a grain mill. [Those who have never been inside a grain mill should visit one; even normal persons can hardly breathe in places where the dust is thick.]

Brown and Colombo[160] point out that the plant doctor is in a particularly favorable position to estimate the effects of work environment and can do pioneer work in discovering industrial causes for asthma. Spoujitch[161] approached the question differently and added the meteorological factors to his analysis of problems in industrial asthma, while Reine[162] discussed the insurance protection problem after presenting a nice coverage on the theoretical causes.

### PSYCHIC INFLUENCES ON ASTHMA

The field of psychiatry is a big one which is undergoing daily changes. It is often difficult to appreciate all the comments made on the relationship

between allergy and psychiatry. Some psychiatrists feel very strongly that psychiatry is the one and only answer, and some allergists believe that allergy is the one and only answer. Fortunately, most allergists and psychiatrists appreciate that, in many cases, if not all cases, both allergy and psychiatry play a role. It will be interesting to know the philosophies of both groups ten to twenty years from now, when the field of cybernetics is better appreciated, and biochemistry in relationship to psychiatry has passed the speculative stage. Perhaps then, a patient's disease and habit pattern will be analysed. For his allergic condition he will perhaps receive some drug which will prevent the formation of specific sensitizing antibodies, and some other drug to correct his "nervous" tendencies. More doctors, however, will agree with Wittich[163] who said, "The better I practice allergy, the fewer psychoneuroses I am forced to treat." [There are probably some psychiatrists who will state the converse.] Burden[154] sums it up nicely by stating that where physical factors predominate the allergist can do the greatest good for his patient by applying sound principles of allergic investigation and therapy, in addition to establishing a doctor-patient relationship which will encourage the patient to speak of his emotional problems. Where psychologic factors either predominate or are the sole cause of the patient's illness, the physician must determine whether he is willing and sufficiently competent to treat the patient, or whether he should refer him to a psychiatrist. Above all, correctly says Burden, the alert allergist should be able to distinguish the true allergic patient from the so-called para-allergic. By so doing, no patient need be subjected to unnecessary psychotherapy or to prolonged and unnecessary allergic therapy. [One problem occurs when the allergic asthmatic patient has a psychiatric factor, but cannot develop insight into the interrelationships; in such a case the psychiatrist may be of no help.]

Dekker and Groen[165] were able to reproduce psychogenic attacks of "asthma" in six of twelve patients. The vital capacity of each patient was measured at four-minute intervals and a base-line value was obtained. An emotional stimulus which was suggested by the patient's history was then administered. The test was considered positive if it was regularly followed by a reduction of more than 10 per cent of the vital capacity. Aspirin-sensitive patients watched someone else swallow an aspirin tablet. Three of these patients developed definite "asthmatic" attacks with pronounced reduction in vital capacity, and three others a transient reduction. These psychogenic attacks were distinguishable from "spontaneous" attacks of asthma or from asthma provoked by inhalation of allergens. The authors believe the phenomena involve a process of acquired conditioning.

Since many asthmatics have been seen by psychiatrists and many psychiatric patients have been seen by allergists, each tries to correlate the history of episodes with pertinent emotional stimuli or meteorological conditions or pollen counts or some combinations of factors. Some pattern to explain the etiology is constantly sought for each patient. Leavitt[166] indicates that asthmatics tend to be emotionally insecure with an intense need for parental love and affection. He believes 98 per cent of asthmatic children suffer from parental rejection. [We presume that he infers that 98 per cent of asthmatic children with emotional conflicts have parental rejection as the basis.] The asthmatic attack should be handled with calm and confidence by the physician. Cluer[167] believes that in a large percentage of asthmatics transient improvement can be achieved by many different methods and therefore a large part of the improvement must be caused by psychological factors. There is hardly any emotional conflict

in a three month old baby with asthma in the early morning, nor in a six year old who has an acute asthmatic attack in a dusty lumber room, but he points out that patterns of mental development remain strikingly similar. If the patients were classified, they would usually be sensitive, intelligent, shy, conscientious, rather nervous and generally good citizens.

McDowell[169] has a healthy approach in his criticism of some workers who, in an evaluation of forty coal miners, suggested that 87.5 per cent of coal miners had varying degrees of disability due to psychiatric illness, and that in 35 per cent it was the exclusive cause of disability, and that asthma occurred in 15 per cent. McDowell states that it is common knowledge that miners have more respiratory difficulties than persons following other trades or occupations. "Naturally a patient having trouble in breathing is going to show some psychoneurotic tendencies. This is true whether he is a farmer, physician or lawyer. . . . I cannot help but feel that, if the authors were to check the lungs of their 'psychoneurotic coal miners' at autopsy, a certain percentage would be found to have an organic basis for their neurosis." McDowell mentions silicosis as frequently present, even in miners with negative chest x-ray films.

Katsch[170] suggests that the cause of a paroxysmal attack of asthma could be by a combination of chemical and psychological factors, and that the latter could act as a trigger mechanism for the conditioned reflex. [This is sound thinking.] Schivers[171] states that allergy in a child is neither a simple disease process nor solely a manifestation of emotional upset but a combination of the two. As such, both aspects should be considered in management. One must keep in mind the concept of the "total allergic load." A heavy blast of psychologic factors may lower a patient's tolerance to the point that minimal weighing of his load of physical allergens will tip the scale toward a full display of his symptoms. Allergic factors which would ordinarily result in only subclinical allergy can produce marked symptoms in the presence of an unresolved emotional problem. Haiman[172] and Garnett[173] have good papers on the bilateral approach which emphasizes the mind and body and the importance of proper timing with medical therapy and psychotherapy.

Baruch and Miller[174] reported on a boy of three with recurrent attacks of asthma, who had numerous positive skin reactions to food and inhalant allergens. Their studies showed no correlation between the attacks and exposures to the reacting allergens. They advanced the thesis that the positive skin reactions were an immunologic response to previous exposures to allergens. Their data suggested that emotional interplay could be correlated to the asthmatic attacks of the child.

Harris[175] disagrees with Baruch and Miller in their claims that maternal rejection is the main cause of allergic symptoms in children possessing an allergic constitution. He points out that instead of emotions causing asthma it is more likely that the asthma frightens the patient and the family and therefore causes various emotional symptoms. [The drugs used, especially epinephrine, ephedrine and aminophylline can also increase the emotional upsets.] He agrees that it is entirely possible that emotional upsets may influence the allergic state by way of the vascular mechanism, but emphasizes that the fundamental etiology of allergic disease is organic, resulting from pollens, environmental antigens, food, fungi and infection. There is no purely emotional allergic disease. The individual attack of asthma or hay fever, for example, may possess a high degree of emotional components, but the person must be basically allergic,

in the organic sense. He points out that if maternal rejection of her asthmatic child is so important then the juvenile homes of the country where children who certainly have been rejected are placed, would be flooded with asthma. Actually in 1954 in San Francisco only five cases of bronchial asthma occurred in 6,986 such children. [By projected rationalization, the psychiatrists could say the juvenile home represents the unrejecting mother figure.]

Garnett[176] expresses his feelings on the mechanism of psychogenic asthma, first stating the pathological reaction is simply an exaggeration of the normal physiologic response to a stimulus. Immunologic and psychosomatic viewpoints are both needed. Asthma is a symptom, the immediate cause of which is a spasm of the bronchioles usually associated with edema and secretion stimulated by either a specific allergen or by more or less specific emotional situations. Either alone can produce an attack, but in most cases both factors operate to a greater or lesser extent varying between individuals and in the same individual at different times. No allergic patient can be adequately evaluated without considering the personality structure [patterns] in which the disease is implanted. Garnett also believes the nuclear psychodynamic factor is the excessive unresolved dependence upon the mother or the mother substitute, which may produce many different character traits [patterns] to deal with this conflict, such as asthmatics who are aggressive, ambitious, hostile, hypersensitive, timid, etc. There is probably no very typical profile but repressed dependency upon the mother produces the defenses. [This is a healthy not too dogmatic approach. His perspective seems broader and as a consequence his remarks can be applied more often.]

Harris and Shure[177] studied the behavior patterns in asthmatic children. On the whole, terms describing behavior such as good or poor social adjustment or work habits are repeated almost exactly the same number of times in asthmatic and control tabulations, with one exception: only four asthmatic subjects especially needed praise or affection in contrast to eleven controls. Emotional factors are believed to be an integral, though not a necessary, part of asthma. Such feelings may result from illness or may act nonspecifically to precipitate or aggravate an isolated attack. Bronchial asthma is affected by other fortuitous circumstances, including change of weather, rising barometric pressure, debilitating disease, and menstruation.

In closing this section, we would like to refer briefly to Jacquelin, et al[178] in their work with allergy and the diencephalon, in which they state emotional disturbances of various kinds may result in the establishment of allergic sensitivity to a wide variety of previously innocuous substances.

## PATHOLOGY

The pathology of bronchial asthma has been well described in past years. The new articles on this subject add very little to our previous knowledge, except as they emphasize the fact that patients with bronchial asthma can die from asthma. Death occurs chiefly in those over forty, but occasionally young adults and even children can have fatal attacks. Educational efforts over many years have finally succeeded in teaching almost all physicians that morphine should not be used in treating asthmatic patients. This indoctrination has undoubtedly saved many lives. Unfortunately, Demerol is still used much too often. We have

completely abandoned its use in our patients because of its morphine-like action in suppressing cough and excretion of sputum and thereby increasing the tendency to suffocation. In addition, Demerol has now become a greater cause of addiction than morphine itself.

The lessening of mortality from overuse of sedatives has probably been offset by a new cause of death in asthmatics, i.e. death directly or indirectly due to ACTH and steroids. These hormones are of great help in treating severely ill patients, and their use has undoubtedly made useful citizens of many pulmonary cripples; we would not like to return to the previous era when they were not available. Nevertheless, some deaths have occurred, and, as is well known, serious side effects can result, e.g. peptic ulcer, mental disease, and a lighting-up of quiescent tuberculosis.

Franklin and his associates[179] report autopsy findings in four allergic patients who were under prolonged treatment with steroids: Case 1, woman, sixty-eight, successfully treated for three years, intractable asthma, apparently died of cardiac failure; Case 2, man, fifty-nine, with asthma and emphysema, five years of steroid therapy, death from recurring pancreatitis. Case 3, man, forty-five, with steroids for four years, developed osteoporosis and collapse of vertebrae with increased pulmonary lesions; Case 4, man, fifty-five, with severe chronic dermatitis developed generalized furunculosis with death from staphylococcic septicemia after one year of steroid therapy.

Crepea and Harmon[180] discuss the significance of membrane changes in asthmatic and nonallergic pulmonary disease. In a series of 116 routine autopsies, 23 per cent showed thickened bronchiolar basement membranes. In 108 surgically-removed lungs the incidence was 32 per cent (all these were from patients with chronic pulmonary disease). In twenty-two asthmatic patients, however, autopsies revealed thickened basement membranes in every case. Thus, while this thickening occurred in other chronic pulmonary disease, it was found in every patient with chronic bronchial asthma. The authors also noted that eosinophilic infiltration was the rule in asthma, but was absent in the nonallergic group of cases.

Guerrant[71] points out that anaphylaxis in animals is not the same as asthma in man. "Patients dying with asthma present a fairly characteristic appearance. On opening the chest the lungs are seen to be overdistended often with localized areas of bronchiectases. The distention seems to be due to actual obstruction in the bronchi or bronchioles. Even if the major bronchi are open, one still can collapse the lung by pressure. A look at the bronchi often shows the cause of this obstruction. Whether large or small, they are seen to be tightly filled with thick mucoid or mucopurulent secretions. Microscopic study often shows thickened bronchial walls. The basement membrane may be hyalinized and the wall may be infiltrated with plasma cells, lymphocytes and eosinophiles. The alveoli are emphysematous, often with stretched or broken walls. Pneumonia is often present. Hyperplasia and hypertrophy of the mucous glands are often present. Hypertrophy and dilatation of the right side of the heart are seen in perhaps a third of the patients dying with asthma. Occasionally frank rightsided heart failure is present."

In a somewhat similar report Cardell,[181] in post-mortem findings in twenty-two cases of bronchial asthma (approximately 1 per cent of the total autopsies in his general hospital over a period of over seven years), noted the following: There were thirteen males, nine females; in eight cases the asthma seemed to be of extrinsic allergic origin, in six after a single pulmonary infection, in eight the asthma seemed superimposed on

chronic bronchitis. While the age of onset ranged from infancy to the seventh decade, the age at death, except for one infant, was from the third to the seventh decades. Those whose asthma began after forty tended to run a short course. Uncomplicated asthma was rarely fatal. [We agree, but there are exceptions.] In twelve of these cases death occurred during attacks of asthma; five patients died from complications or associated conditions; five from diseases unrelated to asthma; and two from asthma alone. Findings at autopsy were strikingly similar to previous reports including plugging of the bronchi by mucus, heavy eosinophilic infiltration, and marked thickening of basement membranes. Cardell, however, emphasized the fact that the more damaged the lungs were, usually by infection, the less the degree of plugging required to cause fatality. In his cases infection was a large factor.

Maxwell[182] reported sudden death in nine asthmatic patients, aged forty-two to sixty-seven, with duration of asthma from five months to ten years; in each patient asthma had started after the age of thirty. The family history was positive for asthma in only two, and skin tests positive in only one. In five of these nine, there was an associated upper respiratory disease. In two patients cardiac conditions were present. Maxwell noted that in each patient death occurred in the middle of what was regarded as an ordinary attack of asthma. In each patient there was a defeatist attitude almost from the beginning of the asthma. Seven patients had expressed a conviction of impending death, and Maxwell concluded that the prognosis is gloomy in those whose asthma begins after the age of forty-five, especially in those who are depressed. [No autopsies were reported in this group, nor the exact medication used, nor any remarks regarding the necessity for a cheerful optimism on the part of the physician and his medical and nursing associates. This lessening of morale suggests Rackemann's "depletion theory." Fortunately, the introduction of steroids has entirely changed the picture; depression in such cases is much less common.]

In another paper, rather similar to that of Maxwell, Leigh and Rawnsley[183] report a mortality of 19 per cent among thirty-two patients whose asthma developed at thirty-five or later. They, too, believe that emotions, especially suppressed anger, are more important at these ages than infection. Obsessional traits of note were found in 34 per cent, and in 53 per cent patients were depressed or anxious. Admission to a hospital usually led to prompt improvement. Leigh[184] also reports death in a thirty-eight-year-old asthmatic woman whose attacks became severe when her mother died. During psychiatric interviews, she showed extreme disturbances associated with weeping; after each interview the asthmatic attack subsided. Following the fourth interview, she slept for the first time in many nights but woke suddenly in status asthmaticus and died within five minutes, despite the use of epinephrine and oxygen. Autopsy revealed typical widespread mucus plugging of bronchi.

Leigh advances this theory: vagal discharge may reflexly be produced by irritation of the nasal, pharyngeal or laryngeal mucosa, by peripheral stimulation as by bronchoscopy or by central stimulation by drugs. In each case, there is a flow of mucus, which, if it becomes excessive, causes death by asphyxiation, since parasympathetic stimulation results in both bronchoconstriction and bronchosecretion. The author states that many asthmatic patients die in psychiatric wards, some of those after psychotherapeutic interviews, suggesting that it is not unreasonable to suppose

that the excessive emotional discharge, probably after a long period of parasympathetic activity, causes the mucus plugging of the bronchi. Atropine should be administered as a routine measure. [This theory is interesting, but the plugging of the bronchi is much more likely to follow exposure to causative allergens. Atropine, in our hands and in others, has been useless. In addition, this patient received three grains of sodium amytal several times during her fatal attack. We have learned, from bitter experience in such cases, to avoid not only morphine and Demerol, but also all strong sedatives and hypnotics. We much prefer whiskey and aspirin, unless the latter is contraindicated, and we do use antihistaminics. Our advice to internes and nurses: we prefer a noisy asthmatic to a quiet dead one.]

Lowell[185] says that death in asthma is due to a widespread obstruction of the bronchial tree by an elastic form of mucus, with probable increase in the tone of smooth muscle in the walls of the bronchi, along with an edema of the mucosa. He believes that this combination is entirely adequate to explain the extreme degree of respiratory embarrassment. Recovery occurs when copious amounts of sticky mucus are expelled, and until this mucus is expelled bronchodilator drugs cannot be altogether efficient.

## CLASSIFICATION OF ASTHMA

As Cooke[186] says, it is difficult to classify allergy, including asthma, in any completely satisfactory manner. He discusses antibodies, antigens, family histories, eosinophilia, immediate and delayed reactions, etc. Every tissue and every organ can become sensitized. Bram Rose[46] also has an excellent article on the problem of asthma. "The diagnosis of asthma is generally not difficult providing one approaches the case in a reasonable manner, takes adequate time to ferret out all contributing factors in the history, and makes a thorough physical examination. The problem is to establish the etiology. The most direct approach in simple asthma consists of identifying the allergens responsible for the symptoms, and either removing them or, when this is not possible, hyposensitizing the patient by one of the accepted methods. Infection and emotional factors can either provoke an attack or under certain circumstances prevent one, and these factors must be recognized and dealt with accordingly. These things having been done, and the various factors evaluated with the aid of skin tests and other laboratory procedures, the majority of asthmatic patients can be adequately treated. Unfortunately, this still leaves quite a number of patients who do not respond, despite all that can be done by these time-proven measures." It is in this group that the use of ACTH and steroids are particularly beneficial.

Swineford[187] states that atopic influences cause about 40 per cent of all cases of asthma; infection alone about 10 per cent; and combined atopy and infection about 50 per cent. The allergic asthmatic coughs himself *out* of an attack, with very little cough during one and almost never before the spasm. The end of the attack is heralded by an exacerbation of the cough which finally becomes productive of glairy mucoid sputum.

Infectious asthma usually follows an upper or lower respiratory infection, with exacerbations with change of weather. Cough usually precedes the wheezing, in fact, as Swineford says, the infectious asthmatic coughs himself *into* an attack. The cough is troublesome before, during and after the attack. In addition to the atopic and infectious types of

asthma there are other causes of wheezing and dyspnea, e.g. cardiac and psychic conditions.

Overall[188] has a nice differentiation between allergic (atopic) and infectious asthma. His table is given in full.

CLINICAL COMPARISON OF ALLERGIC (ATOPIC) AND INFECTIOUS ASTHMA (Overall, J.C.) (188)

| Allergic (Atopic) | Differential Criteria | Infectious |
|---|---|---|
| | *History* | |
| Predictable often | Season | Cold and changeable |
| Late in attack | Cough | Prominent, early |
| No residual | Cough | Residual |
| Mucoid, early or late | Sputum | Purulent |
| Mucoid, early or late | Nasal discharge | Purulent |
| Foods and inhalants | Precipitating factors | Respiratory infection |
| Frequent | Other allergy | Infrequent |
| Frequent | Sneezing | Infrequent |
| Frequent | Itching eyes | Infrequent |
| Absent | Lacrimation | Infrequent |
| No effect | Fever | Common |
| Good | Antibacterial therapy | Shortens or aborts |
| | Response to adrenalin and aminophylline | Fair to poor |
| | *Physical Examinations* | |
| Pale swelling | Nasal mucosa | Red, swollen |
| Mucoid | Nasal secretions | Purulent |
| Pale translucent | Uvula | Red, wrinkled |
| Pale | Tonsils | Red or normal |
| Pale | Lateral pharynx | Red streaks |
| Asthma | Chest | Asthma |
| Transilluminate | Sinuses | Often opaque |
| | *Laboratory Data* | |
| Clear or thick mm. Symmetrical | | Opaque—hazy, often unilateral |
| Normal | Sinus x-rays | Elevated or normal |
| Infrequent | Leukocytes | Common |
| Foods and inhalants Prominent | Eosinophilia | Foods and inhalants not prominent |
| | Skin tests | |

Rapaport[189] also discusses classification of asthma. He deplores Chevalier Jackson's statement that "All is not asthma that wheezes" as being too constrictive. Asthma, he says, is due to many causes, including the antigen-antibody reaction. "Causes other than allergy may initiate or express themselves in asthma." "Atopy and infection are usually the most significant primary factors." "The asthma syndrome, according to Peshkin (Progress in Allergy, edited by P. Kallos, New York, Interscience Publishers, Inc., 1952, chapter 56), may be divided into three stages (especially in children). 1. The oppression stage is a subjective complaint voiced by patients and consists of a feeling of tightness or heaviness in the chest and difficulty in breathing deeply. Examination of the lungs reveals them to be clear. No wheezing is audible. 2. The wheezing stage or pre-attack stage is often diagnosed wrongly as bronchitis or asthmatic bronchitis. The characteristic sibilant and sonorous rales are heard at this time. Dyspnea may or may not be present. 3. The attack stage epitomizes the summit of the asthmatic syndrome. Dyspnea is very troublesome during this stage of asthma. The musical rales are very pronounced. The wheezing may be audible at a distance. Frequently, the posture of the patient is characteristic. In some cases, despite adequate drug therapy, the attack stage may persist for longer than forty-eight to seventy-two hours, and this phase is termed status asthmaticus. Should asthma be relatively continuous and the intervals between attacks short in spite of competent allergic management, then such cases are designated

as chronic or intractable asthma. Thus, essentially, status asthmaticus and intractable asthma are distorted forms of the third stage of asthma—the former implying a relatively acute severe state and the latter, a chronic state present over a long period of time."

Other articles regarding classification came from Sullivan,[190] who discussed allergy from the immunologic point of view; Hartman,[191] with a survey of the present position of allergy; and Costa,[192] with a discussion of nomenclature and mention of psychotherapy and hypnotism.

### SYMPTOMATOLOGY

Lowell, Schiller and Lynch[193] have estimated daily changes in the severity of bronchial asthma. Five patients were observed at intervals of one week or less over a period of approximately six months. Simple tests of pulmonary function were carried out at intervals of about one week or less. Each patient kept daily records of his medication, symptoms, and activities. The data were then converted to a numerical score as a measure of the intensity of asthma for each twenty-four-hour period. When this score was compared with pulmonary function measurements the correlation was usually striking. Results of the study: no single criterion can serve as an accurate measure of the severity of bronchial asthma. A more reliable estimate is possible when the intensity of symptoms, the amount of medication required, and the results of simple pulmonary function studies are taken into account.

In Marley's work,[194] groups of asthmatics from a general and a psychiatric hospital were compared with one another and also with groups of normal and neurotic individuals from the same locality and of about the same age and sex. All subjects completed the Cornell Medical Health Questionnaire. From an analysis of the total responses the results: male asthmatics seen at the psychiatric hospital were about the same as male neurotics. Male asthmatics from the general hospital were significantly different from both normal and neurotic controls, falling between the two. In contrast, the two female asthmatic populations were identical in their responses, being significantly different from both groups of normal and neurotic controls. The analysis demonstrated that all groups of asthmatics were significantly more inadequate and tense than normal controls, while those asthmatics under psychiatric treatment showed no significant difference in their responses for depression, anxiety, sensitivity and anger from the neurotic controls.

Banyai and Joannides[195] stress the importance of distinguishing between helpful and harmful coughs. Cough can be hazardous in many ways, including interference with healing of inflammatory diseases of the bronchi and lung parenchyma; interference with rest; rise in temperature; dyspnea, exhaustion, headache, subconjunctival hemorrhage, insomnia, anorexia, vomiting; urinary incontinence; postoperative disruption of wounds of the anterior abdominal wall; pain in the chest; fractured ribs; possible droplet spread of infection from one part of the lung to another or from one lung to the opposite side; pulmonary hemorrhage; bronchiectasis; bronchospasm; lowering of the threshold of cough irritability; mediastinal emphysema, spontaneous pneumothorax, subcutaneous emphysema; cervical hernia; so-called hypertrophic emphysema; strain on right ventricle; and tussive syncope or its formes frustes. [Fractured ribs have occurred in a fair number of our asthmatic patients. The violence of cough in some asthmatic is so extreme fracture can readily occur.]

Turiaf et al[168] found hemoptysis in 6 per cent of his 1,500 cases, but in 15 per cent there was associated pulmonary tuberculosis, heart failure or bronchiectasis. [His percentage, therefore, is probably much too high as regards uncomplicated bronchial asthma. Traces of blood in the sputum are fairly frequent in our uncomplicated cases, but frank hemoptysis strongly suggests some complication.] Bachman and Ruiz Moreno,[196] in forty-eight attacks of asthma in thirty patients, found that sputum examinations often revealed an important infectious element.

Enger[197] found sputum eosinophilia in all of seventeen patients with bronchial asthma, and in none of thirty-two individuals who had non-allergic pulmonary disorders. In these seventeen, however, blood eosinophilia was only present in five. Enger concluded that eosinophilia in the sputum is a more reliable sign of bronchial asthma than is blood eosinophilia. [We are not entirely convinced that this is true; we have had fairly high sputum eosinophilia in pulmonary cases without definite evidence of allergy.]

Interesting answers to a query[198] regarding high eosinophilia (23 to 38 per cent) in an asthmatic child of two and one-half-years: Both consultants agreed these percentages are high but can occur in young children; both pointed out the necessity of searching for other possible causes, e.g., Loeffler's syndrome and parasites. One consultant noted that "Vaughn in British East Africa recently reported interesting observations in experimental eosinophilia (Vaughn, J.: Blood 8:1, 1953). He traced the path that the eosinophil probably follows in its journey through the body. From the bone marrow it travels in the blood stream to the lungs or intestines, where, leaving the blood vessel, it makes its way through the tissues to the mucosa of the bronchus or intestine. At this point in the lung at any rate, it either passes into the lumen of the bronchus and is eliminated from the body or is caught up in the lymphatic system, whereby it may re-enter the blood stream, from which it is extracted and subsequently destroyed by the spleen. It is highly probable that the function of the eosinophilic leukocyte is to carry histamine or a histamine-like toxic material from the bone marrow to the tissues for inactivation. This concept provides a common factor among the widely varied clinical conditions with which eosinophilia of the blood is associated in man and offers an explanation of the clinical syndrome of eosinophilic infiltration of the lungs."

Silbert and Worne[199] studied the synergistic relationships of pyridoxine (vitamin B6) with the unsaturated fatty acids in the allergic state, especially bronchial asthma. Asthmatics were given a special experimental formula four times daily, including Vitamin A, thiamine, riboflavin, phosphoric acid, pyrodoxine and calcium panthothenate. After ninety days only 40 per cent were benefited; the best results were obtained in those who were also being hyposensitized. The pyrodoxine was probably a good adjuvant to therapy. According to Storck,[200] the number of thrombocytes in peripheral blood is reduced 15 to 40 per cent within ninety minutes after exposure of an allergic patient to the causative allergen (food, inhalant, or drug, as well as infectious).

The *C-reactive protein* in asthma, et cetera, has been studied. Kaplan, Aaronson, Henderson and Goldin,[201] in a good study, point out that a precepitin test has been developed for detecting the presence of this protein, a substance not found in the blood of normal persons. The presence of this C-RP parallels the erythrocyte sedimentation rate as an indication of rheumatic activity and may be used to measure other

manifestations of inflammation. In 101 asthmatics (ages five to seventy-one): in the infectious group (thirty-five patients), eight showed the presence of C-RP precipitations and six had positive anti-streptolysin 0. titers (A.S.O.). In the atopic (non-infectious) group (twenty-seven patients), all had negative C-RP reactions, while nine gave positive A.S.O. titers. In those with both allergy and infection (thirty-nine patients), there were eight with positive C-RP; fourteen with positive A.S.O. titers. Kaplan et al conclude, therefore, that the A.S.O. titers were of little value, whereas the C-RP determinations were helpful in differentiating infectious from non-infectious asthma.

In another article Aaronson and his associates,[202] in 201 allergic children and 1,003 allergic adults, again found the C-RP much higher in infectious asthma, as compared to atopic patients, with mixed cases in an intermediate position. The findings were more clear cut in children. Patients with infectious asthma who had had recent upper respiratory infections were found frequently positive for C-RP. In a control group of forty-three nonallergic children there were no positive C-RP reactions following upper respiratory infections.

Roantree and Rantz[203] agree that the C-RP is a sensitive index of an inflammatory or necrotizing process in the body, but in active tuberculosis the erythrocyte sedimentation rate more accurately reflects the clinical state. The test is negative in bronchial asthma unless there is associated secondary bacterial infection. Smith and Skaggs[14] agree that the C-RP test is of little value in allergy (except in urticaria). Of 100 patients with infectious asthma, fourteen had C-RP values of 2 plus or higher, and in all but two of these fourteen some other condition co-existed.

Tuft and Scherr[204] tested eighty-five children and twenty-four others, with simultaneous chest x-rays. They showed a lack of correlation between sedimentation rates and the C-RP reactions. The C-RP reactions were usually positive in cases of active rheumatoid arthritis, active rheumatic fever, and in those whose x-rays indicated pneumonia. Their studies failed to confirm the suggested role of that test in the etiologic diagnosis of asthma. The test is positive as often in febrile patients whose asthma is quiescent as in those whose asthma is active.

[From these studies it seems obvious that this new test is of little additional value in asthma or other allergic diseases. To us the routine determination of the sedimentation rate in asthma is a must, as an increase over normal values (up to nine in males and twenty in females) almost always indicates either an infectious complication or some associated condition, e.g. cholelithiasis.]

Westergren,[206] in a study of 6,000 cases of pulmonary tuberculosis and 691 cases of non-tuberculous pulmonary diseases, found a great increase (in the tuberculous group) of serum titres (antistreptolysin titre regarding beta-hemolytic streptococci and the anti-staphylolysin titre for yellow staphylococci). In asthma and lung carcinoma there was only a low rise in titres. Cases with signs of bronchostenosis, both tuberculous and nontuberculous, exhibited roughly a 50 per cent higher incidence rate, as compared to those without bronchostenosis.

## COMPLICATIONS

*Complications* can occur in patients with bronchial asthma and, of course, therapy must necessarily include care of the asthma and the complication.

Rakower et al[207] reviews the literature on massive atelectasis in asthma, and reports two new cases, with recovery, one in an eight-year-old boy, the other in a girl of fifteen. Recovery occurred in four to ten days in the boy and within six days in the other patient. Abram and Frankel[208] reported four cases of middle lobe syndrome in allergic patients. Early diagnosis is necessary, along with prompt therapy (broncho-dilators, expectorants and antibiotics). The early care prevents the onset of atelectasis and/or bronchiectasis, and also makes lobectomy unnecessary. The authors feel that the mechanism of the collapse is bronchial allergy and its resultant inspissated mucus occluding the bronchioles, followed by secondary infection and production of complete obstruction of the smaller air passageways. The relief of the edema and bronchiolar obstruction gave gratifying results in all four patients. Neither bronchoscopy nor surgery was necessary. The series included three adults and one boy of nine; all had respiratory allergies and positive skin tests. [Inhalation of Tryptar has been of excellent help to us in similar cases; others prefer detergents by inhalation, e.g. Alevaire®.]

Henry[209] reports a case of subcutaneous emphysema in a six-year-old asthmatic child, with recovery in six days. Air reached around the neck, into the axilla and even down the left flank, and cyanosis, dyspnea, et cetera, were very severe. Turiaf, Marland and Mathieu,[210] in an analysis of 2,000 adult asthmatic patients, found three with mediastinal and subcutaneous emphysema, and twelve with spontaneous pneumothorax; of these, two also had subcutaneous emphysema. Most of these complications occurred between the ages of twenty and thirty, and usually followed severe paroxysmal asthma. Pain in the chest and increased dyspnea were the main symptoms. The pneumothorax was usually on the left side and was re-absorbed in fifteen to twenty days, but one patient with unilateral pneumothorax died. Pleural effusion occurred in four cases, and was usually slight and gone in six to ten days. The pleural fluid was rich in eosinophiles in contrast to a moderate blood eosinophilia. In six of the patients with pneumothorax emphysematous blebs were found (by x-ray in four, by pleuroscopy in one, and by post-mortem in one).

Rupture of the eosophagus occurred in two patients as a complication of status asthmaticus. This hitherto undescribed and usually fatal complication, according to Mitchell, Derbes and Akenhead,[211] was caused by severe vomiting. The onset was sudden, and usually preceded by emesis, with violent pain in the epigastrium and precordium, often associated with tenderness or rigidity of the abdominal wall. Certain postures may lessen the pain, but breathing, swallowing and body movement aggravate. Thirst and voice alteration occur, and subcutaneous emphysema is usually first noticed in the neck. These symptoms and findings should distinguish esophageal rupture from coronary occlusion and perforated peptic ulcer. Only prompt surgical intervention can save the patient's life.

Acute diffuse pneumonia occurred in sixteen asthmatics, according to Felson and Felson.[212] It is occasionally fatal; in the one autopsy there was an acute diffuse suppurative bronchiolitis and nodular peribronchiolar pneumonia. This complication occurred at an average age of forty-seven; onset was apt to be abrupt; fever, dyspnea, wheezing in some cases, leukocytosis without eosinophilia, and mucopurulent sputum were noteworthy.

Myocardial infarction is a not infrequent complication in older asthmatic

patients. Usually the symptoms and findings of each are fairly clear cut, but sometimes the diagnosis of both conditions is not too easy, and therapy is difficult. As stated in an answer to a query[213] it is essential to lessen the asthma because of its damaging effect on the heart. Steroids and ACTH should be used in severe asthmatics in such cases.

### EMPHYSEMA

As pointed out by Lowell,[36] whom we quoted in the section on Immunology (q.v.), there is some confusion as to the relationship between emphysema and chronic bronchial asthma. We agree with Lowell's statement that "the pathogenesis of asthma and emphysema (the so-called obstructive pulmonary irreversible type) has important similarities and clinically the features of the two conditions overlap so strikingly as to make it impossible to draw a line between them. All the abnormalities of ventilation which have been described in emphysema are also demonstrable in asthma."

It seems to us that the best way to discuss emphysema is to divide it into two main groups: (a) the emphysema which is due to chronic bronchial asthma and, in fact, is really a part of it; and (b) the other types of emphysema which are not allergic and not at all related to true bronchial asthma. In almost all patients whose emphysema follows bronchial asthma there is some personal and/or family history for allergy, blood and sputum eosinophilia is common, and skin tests usually give good to excellent reactions. In the other groups, however, those findings which suggest allergy are usually absent. Most emphysematous patients have the post-asthmatic form or the other, but it is possible for one with chronic bronchial asthma to develop emphysema both from his asthma and from other exposures, e.g. some form of pneumoconiosis.

The distinction between the two groups is important because in post-asthmatic emphysema the prognosis for improvement and for length of life is good, and therapy is chiefly directed at the causative allergens. In young asthmatics, this type of emphysema is frequently reversible, but as age increases reversibility becomes less and less frequent.

In the other group not due to asthma, the disease is usually irreversible from the onset; in fact, this type of emphysema tends to become progressively worse, despite all types of therapy, even including ACTH and steroids.

Unfortunately, the papers on emphysema we are about to discuss are so written as to make this division impossible.

The subject of pulmonary emphysema has drawn many articles and the fine book by Barach and Bickerman.[18] In the older age group Barach[214] has also done well in emphasizing the hazard of over-conserving energy. Inertia leads to atrophy of the muscular system and of the more complex glandular and psychologic factors. Necropsies on patients with diagnoses of pulmonary emphysema or heart disease sometimes reveal no traces of these clinical entities, but instead a simple wasting process due to atrophy which inevitably results from the over-conservation of energy. Cardiologists are now saying that people are being killed by bed rest. Barach advises patients with emphysema to exercise and build up their pulmonary reserve by a walking program while breathing 10 liters of oxygen per minute through a plastic cannula. Eventually such patients are able to exercise with less dyspnea even when breathing ordinary air. In addition, he advises prednisone because it makes possible an

increased amount of exercise, as demonstrated in more than 100 patients. He also advocates diaphragmatic breathing, diaphragmatic belts, care of any bronchospasm and nervous factors, et cetera.

Burgess[215] also reviews emphysema especially in geriatrics. One must compare the dyspnea only with the expected dyspnea at that age, not by comparison with previous activities. Dyspnea while talking or dressing is especially significant. Emphysematous patients usually prefer to lie flat, while patients with heart failure sit up. [We must add that the asthmatic emphysematous patient sits up when asthma is present.] In therapy one must try to control such complicating or causative factors as asthma, chronic pulmonary disease and obesity. Smoking is forbidden. [We agree and even urge our asthmatic and emphysematous patients to avoid the tobacco smoke from others, as well as all other types of smoke and fumes.] Burgess also advises avoidance of excessive amounts of rest.

Ebert[216] measured pulmonary elasticity which is the sum of several factors, including the elastic tissue found in the alveolar walls, the blood vessels and the pressure within them, and the surface energy of the air liquid interface. In patients with pulmonary emphysema the pressure volume curves are shifted upward, indicating greater lung distention at a given pressure than in normals. This is based upon an increase in residual volume. The dyspnea in emphysema is related to decreased maximal expiratory air flow. The rate of air flow depends upon the pressure gradient between mouth and alveoli and the resistance to flow. As long as intrathoracic pressure is negative, an increase in pressure causes increased air flow; when intrathoracic pressure becomes positive, further increases in pressure no longer lead to increased air flow. This "check valve mechanism" is a result of collapse of the bronchioles when intrathoracic pressure becomes positive. It is this factor which causes the dyspnea in pulmonary emphysema; since the bronchi are supported by cartilage they do not collapse, even when partially obstructed, as in asthma.

In cardiac patients, on the other hand, dyspnea is related to reduction in vital capacity and demonstrates a lower pressure volume curve than in normals. Increased pulmonary blood volume decreases vital capacity; pulmonary vascular pressure and pulmonary edema also contribute to these alterations.

Guerrant[217] has a good summary of the pathologic physiology of pulmonary emphysema. "Most of the abnormal physiology in emphysema is a result of bronchial or bronchiolar obstruction. The bronchial disease may be the result of chronic allergy, chronic infection, inhalation of irritants, or chronic anxiety. It may lead to impaired ventilatory function, overdistention of the lung, poor oxygenation of the blood, retention of carbon dioxide, polycythemia, pulmonary hypertension, and cor pulmonale. Effective treatment is directed toward relief of bronchospasm, clearing secretions from the airways, improvement of function of the thoracic cage, and control of heart failure."

Scarrone et al[218] did vital capacity studies with both the Benedict-Roth and McKesson-Scott spirometers. Subjects breathed slowly and steadily after a maximal inspiration. The best of three successive determinations was termed the "slow" vital capacity. After a rest period of five to ten minutes, patients exhaled as rapidly as possible into the apparatus. The best of three determinations was called the "fast" vital capacity. The authors found that (a) in forty healthy controls (average age forty-one) the range between the two was minus 5 to plus 5 per cent

in thirty-seven cases; in another thirty-five individuals free from cardiac or pulmonary diseases but whose average age was fifty-six, the range in twenty-four was the same, but in the other eleven was from minus 15 to plus 20. (b) In thirty patients with bronchial asthma, of whom two also had emphysema, and with an average age of forty-eight: in sixteen the range was again from minus 5 to plus 5 per cent; the remainder showed varying degrees of difference in the "slow" and "fast" vital capacity readings, in some cases up to 50 per cent. (c) In sixty-seven patients with obstructive pulmonary emphysema, with or without bronchospasm: 103 tests were made on these patients whose average age was sixty. In twenty-six (25 per cent of the total tests), the difference was again between minus 5 and plus 5 per cent. The remainder (75 per cent) showed marked variations, the highest being 126 per cent. Although x-ray studies did not correlate too well, the greatest divergencies occurred in patients with the most advanced emphysema.

Rushing[219] estimated pulmonary disease in a different way. In a study of 264 persons, with both normal and abnormal lungs, the degree of pulmonary expansion and contraction was shown by the technique of using standard measurements of posterior-anterior and lateral roentgenograms of the chest on full expiration and full inspiration. This method gave an estimate of the ratios of the residual to the total lung areas, and enabled him to detect abnormal breathing patterns in the early stages of emphysema. His results from these radiologic measurements compared closely with those obtained by the spirometer (as opposed to the lack of correlation mentioned in the previous paper). Rushing claims these advantages for his method: (a) an accurate basic roentgenographic examination of the lungs; (b) early recognition of disordered breathing patterns; (c) permits estimation of the ratio of total lung capacity to residual volume; (d) permits a radiographic estimation of vital capacity: (e) provides a guide to evaluation of results of therapy; and (f) provides a permanent numerical and pictorial record of the progress of the patient. [This technique is a good one, especially in those who for some reason or other cannot adequately use the spirometer. Repeated x-ray exposures, however, may not be harmless.]

Feffer and Mann[220] discuss therapy for pulmonary emphysema; they emphasize the need for relief of obstruction (nebulization of oxygen, sympathomimetic drugs, detergents, et cetera), and control of infection. Lister [221] points out that asthma, chronic bronchitis and emphysema should be looked on not as separate entities but as an integrated sequence of pathological change. Lopez-Botet and Vicente Gil,[222] from Spain, believe that the dyspnea in emphysema is only in part related to organic bronchial stenosis. Neurologic mechanisms play the outstanding role in causing inspiratory and phrenic spasm that can be controlled through the use of oxygen and electroshock. In juvenile asthma there is a clearcut relationship with the degree of bronchial stenosis; in emphysema, say the authors, phrenic spasm is predominant. Among other papers which discuss emphysema are those by Miller[223] on current concepts in diagnosis and treatment; and by Attinger et al.[224]

Sluiter and Orie[225] studied fifty-six patients with emphysema, of whom forty-nine had a history of bronchial infection, forty-six asthma and/or hay fever, and twenty-eight bronchiectasis. Cardiac decompensation occurred in twenty-two, and right ventricular hypertrophy was revealed by electrocardiograms in fourteen of these twenty-two. The authors state that mechanical factors do not, as a rule, cause right heart failure in

emphysematous patients. Functional disturbances, especially hypoxia, are much more important. The amount of hypoxia depends on the severity and extent of the chronic pulmonary infections and of the superimposed acute pulmonary infections. The hypoxia causes pulmonary hypertension. Coronary sclerosis, pulmonary fibrosis and asthmatic factors definitely increase the tendency to decompensation, but rarely do they cause decompensation by themselves. Infection seems most important. None of their twenty-two patients who went through twenty-eight episodes of decompensation died in the course of decompensation.

[As we have often stated, patients with severe bronchial asthma, even with resultant emphysema, very rarely develop cor pulmonale unless there is also present some other pulmonary condition, e.g., advanced bronchiectasis, pulmonary fibrosis, some type of pneumoconiosis, or high-grade kyphoscoliosis. Left heart failure rarely occurs in patients with bronchial asthma unless there is some associated cardiorenal condition, e.g., hypertension, nephritis, valvular heart disease, or coronary occlusion.]

Cor pulmonale has been extensively studied by Hecht,[226] with discussion of its nature, diagnosis and management of both the decompensation and the underlying pulmonary condition. The treatment of heart failure in cor pulmonale "differs in no way from other types of heart disease." Appenzeller and Benz[227] also stress the treatment for the responsible pulmonary diseases. Orthopnea is rare but cyanosis common. Enlargement of the pulmonary conus is the earliest sign of right ventricular hypertrophy. "Prevention and prompt treatment of acute respiratory infection is the main aim in the management of patients with cor pulmonale." Antibiotics form an "essential part of treatment" in the presence of cardiac failure.

Two papers emphasize the not infrequent occurrence of benign peptic ulcers in patients with emphysema or other chronic pulmonary disease. There are no known reasons for this correlation, but Weber and Gregg,[228] in a five-year-study from a Veterans Administration Hospital, found such chronic lung disease in thirty of seventy ulcer patients. A control study of non-ulcer patients in the same age group from the same hospital showed that only 10 per cent of 500 patients had chronic pulmonary disease. Latts et al,[229] from another Veterans Administration Hospital, report that peptic ulceration was proved radiologically or by postmortem examination in about 20 per cent of 586 emphysematous patients; an additional 20 per cent had symptoms or signs but no radiologically demonstrable ulcer crater. This incidence is 3.6 times higher than expected; the association is, therefore, significant. The authors advise caution with steroid therapy for those with emphysema else the incidence of ulcer will rise even higher. Subtotal gastric resection or vagotomy might be necessary in an asthmatic patient who really needs steroids but who has an associated ulcer.[230]

### BRONCHIECTASIS

The relationship between bronchiectasis and bronchial asthma is still disputed. Is there a cause and effect relationship? Huizinga[231] is convinced that allergy is of great significance as a cause of the bronchiectasis of the diffuse basal type. He mentions the changed bronchial secretions in asthmatic patients and the influence of these secretions on ciliary movements. He does not believe that there is an infection route through direct aspiration from the nose and paranasal sinuses. Fisher and Pratt[232]

state that bronchiectasis with chronic bronchial infection is a most important reason why many asthmatic patients do not respond to ordinary anti-allergy therapy. When there is no response one must look for some complication, especially infection. The authors have experience with 105 bronchograms, with only four reactions, of which two were in the form of rashes, one with a bullous eruption, one with parotitis. There is a reversible "pseudobronchiectasis."

Beattie[233] says that in bronchiectasis dilated damaged bronchi are surrounded by acute or chronic inflammation. Atelectasis, pulmonary fibrosis, pneumonia, emphysema and pleural adhesions may be associated. Bronchial obstruction and infection are the principal underlying causes, and therapy is necessarily directed against these two. He discusses postural drainage, the use of potassium iodide, antibiotics, expectorants, and excision of the affected lung tissue.

Wollman, from Israel,[234] states that "Two important factors are acting in the pathogenetic development of bronchiectasis. The first is pressure on the walls of the bronchi which may be due either to air pushing the wall or to traction from the outside; the second factor is the weakening of the resistance of the bronchial wall which is practically always caused by inflammation and subsequent degeneration of the statically important bronchial structures. Both factors are acting in some cases of bronchitis and bronchopneumonia, and especially in those where the spread of micro-organisms is interstitial, i.e., in peribronchial and interstitial pneumonias. Pathologically, bronchiectasis is usually accompanied by bronchitis, peribronchitis, areas of atelectasis, areas of emphysema, and an interstitial exudative or fibrosing process.

"The pathology of bronchial asthma is imperfectly known as only the most severe attacks cause death. It is interesting to note that in patients dying from asthma there is usually bronchitis and peribronchitis as well as interstitial pneumonia and fibrosis." [Such statements need confirmation. In our experience the presence of such severe infections is not necessary as a cause of death in bronchial asthma.] It seems possible, says Wollman, that "in some cases the same factor causes both these entities.

"Bronchiectasis, with the infected foci it helps to create, may cause endogenous allergy to the micro-organisms and debris which stagnate. On the other hand, the reduction in the respiratory capacity of the bronchiectatic lung (due to atelectasis, emphysema, fibrosis, and severe sclerotic changes in the blood vessels) may precipitate attacks of dyspnea, and lower the threshold below which true asthmatic attacks develop."

[We see many patients with bronchiectasis; wheezing is associated in many of these but with no other evidence for the diagnosis of true bronchial asthma. In others bronchiectasis and bronchial asthma co-exist. We do not recall patients in whom bronchial asthma precedes bronchiectasis; hence we believe, with Mallory,[235] who stated that, in a group of sixty patients with bronchial asthma that he personally studied, bronchiectasis was so exceptional that it appeared to be coincidental.]

Strang[236] studied the fate of children with bronchiectasis. Follow-up studies in 1950 were carried out on 209 children (under the age of fifteen) who were admitted to the Newcastle Regional Thoracic Surgery Center between 1935 and 1948, with therapy completed by the end of 1948. There were 119 girls and ninety boys, with initial symptoms commencing before the age of five in 75 per cent; in eighty the symptoms began during the first year of life. Pneumonia was the initial illness in

seventy-four; measles, pertussis or acute bronchitis in eighty-one; unknown in sixteen. Asthmatic symptoms occurred in fifty children, usually as an occasional wheeze, but only eight children had frank asthma attacks. Sinus infection was present in fifty-nine of one group of ninety-two, and sinusitis in 80 per cent of forty-four children who had bilateral bronchiectasis, and in 50 per cent of forty-eight patients with unilateral.

The results of surgery (163 cases) and conservative therapy (forty-six cases) were compared. The mortality from surgery has become less and less. He had only one death in nineteen pneumonectomies and 173 lobectomies or segmental resections during 1949-1951 (in the earlier days there were twenty-four surgical deaths). Seven patients with frank asthma had surgical procedures and all did *badly* with persistence of their asthma. Of six children with constant pre-operative wheezing, three lost their wheezing. Of twenty-six patients with only nocturnal wheezing, fourteen have lost all signs of asthma, nine have intermittent wheezing, and three have died. Pneumonectomy seems especially bad for asthmatic children. [Nowhere in this article is there any reference to allergic workup or allergy therapy, which would improve the prognosis. This is a fine detailed report, but it certainly demonstrates that removal of bronchiectatic tissues, while often definitely indicated will seldom relieve any associated bronchial asthma.]

### ASSOCIATED CONDITIONS

An asthmatic can have not only complications from his asthma, but also can have all sorts of associated conditions common to mankind. Many of these associated diseases aggravate the asthma to such a degree that hospitalization is necessary, and one must treat accordingly. As these lines are being written, for example, our patients now in the hospital are all asthmatics, but, in addition, one has aortic regurgitation and decompensation; another, coronary occlusion, decompensation and bronchiectasis; two have pneumonitis; one child probably has a foreign body; an adult has a subacute maxillary sinusitis; another, bronchiectasis plus foot drop; and one with apparently uncomplicated bronchial asthma. Thus only one of eight hospitalized asthmatic patients seems to be free from other diseases; certainly more than 50 to 75 per cent of those we send to the hospital have one or more other conditions. One can therefore see how essential the study of internal medicine is to the allergist (and vice versa).

Pulmonary tuberculosis can occur with asthma. In fact, one specimen of sputum can show both tubercle bacilli and eosinophilia. An answer to a query[237] states that "the incidence of bronchial asthma in patients with pulmonary tuberculosis is identical with its incidence in the general population. This represents true allergic bronchial asthma, with the sensitivity being due to the common antigens, and does not represent an allergic manifestation to the tubercle bacilli. The conventional treatment for asthma is indicated and should produce results uniform with those obtained in nontuberculous patients. The only exception to this statement is that steroid therapy should not be used in those patients having known tuberculosis or in those suspected of having tuberculosis." [Exception can be taken to this last statement. If a patient with known tuberculosis has very severe asthma which has not yielded to usual therapy, ACTH-aminophyllin intravenous drip should be given until

the attack is over, along with appropriate measures for the tuberculosis. Prolonged use of steroids, however, can be very harmful.]

Van Ufford[238] discusses hypertension in association with asthma, along with case reports. The prognosis is necessarily poorer in such patients and the hypertension demands the usual therapy. Low blood pressure is definitely not the rule in bronchial asthma. Chiari and Zandanell[239] report a case of acromegaly along with asthma.

Allergic rhinitis and sinusitis are frequently present along with bronchial asthma. Maunsell[240] from England, found asthma in 24.5 per cent of 271 patients with seasonal or nonseasonal allergic rhinitis. The asthma sometimes precedes the pollen hay fever. [In the United States hay fever and perennial allergic rhinitis usually precede asthma.] The size of inhaled particles is an important factor. Those of a diameter of 3 to 10 microns will be deposited chiefly in the bronchi and bronchioles (in this range are included the smaller spores and the smaller dust particles). Maunsell found nine million dry rot spores per cubic meter in an old house in London. Vukobratovic[241] notes the close relationship between the mucosa of the nose, nasal sinuses and bronchial tree; equal exposure occurs with various external offending agents. In 100 cases of allergic rhinitis in his native Belgrade, Yugoslavia, hay fever was present in 12 per cent, vasomotor rhinitis in 88 per cent, and bronchial asthma was also present in 80 per cent. The author sprayed fifty patients with vasomotor rhinitis with 0.3 mg. histamine; twenty-seven developed violent rhinitis and the other twenty-three edema without secretion.

The relationship between infectious sinusitis and asthma is still somewhat puzzling. Siegel et al[242] studied eighty-two patients with bronchial asthma; all had sinus studies to determine the role of sinus infection. Allergic, rhinologic and sinus x-ray examinations were made, together with microscopic and bacteriologic studies of nasal and sinus secretions.

The results: The fifty-eight patients with "intrinsic" asthma showed sinus infections in twenty-five; no infection in thirty-three. In the twenty-four patients with "extrinsic" asthma only five showed infection. Of forty-four with positive x-rays twenty-four showed sinus infections. The other twenty-nine patients in this series gave negative x-ray findings. In sixteen "intrinsic" cases, antral membranes were removed.

The authors conclude: sinus infection is *not* a primary cause of asthma, but rather a complication superimposed on altered sinus membrane. In the management of the sinus disease conservative measures should first be undertaken, and later only such surgery as is indicated by local naso-sinal abnormalities or by persistent infection. In sixty-one asthmatics who had sinus surgery one to fourteen years previously, with or without radical operations: definite improvement in the asthma occurred twice as often in the group without removal of antral membrane; actually, only a few in either group were benefited. Postoperative improvement is very unpredictable.

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*(To be continued in September-October issue)*

# Editorial

*The opinions expressed by the writers of editorials in the* ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

## ALLERGISTS ARE MADE—NOT BORN

There are, at present, many types of "allergists." In one community, the allergist may be someone interested in allergy and perhaps the only available physician who has ever attended a seminar or a postgraduate course. In another, he may be a well-trained allergist who truly searches for authentic allergenic causes of his patients' disorders and is equally familiar with the nonallergenic disorders which allergy may mimic. He then re-refers patients whenever the present disorder mimics allergy but is not truly allergic. The allergist may be a physician who ascribes all illness to allergy or to one aspect of allergy and is, what might be termed, unevenly trained.

The allergist is sometimes a "practical allergist," who knows how to test and treat pollenosis, but who knows little else except perhaps the treatment of moderate, uncomplicated bronchial asthma. He may secondarily practice allergy, as when he is primarily a pediatrician, an ear, nose and throat specialist, a dermatologist or psychiatrist, not that these specialists cannot and do not often practice superlative allergy. He may otherwise be an *internist,* as widely practiced in general medicine as in some of the special aspects of the vast field of allergy.

A physician who wishes to refer a patient for studies has no way of judging the quality of the allergy practiced by the allergist into whose hands he has placed his patient's present treatment and future welfare.

If he will, he can choose his allergist from among the Fellows of the two national Societies. A moment's reflection proves that this is not enough. The qualifications for Fellowship in these societies have, in the past, as they have for all similar societies, occasionally varied, and sometimes been dictated by motives other than the physician's qualifications. We are all of us familiar with the fact that in every national society we know, physicians have sometimes been retarded or advanced on the bases of personal likes and dislikes, rivalry, jealousy, and, rarely as well, for reasons of religion, race and color. This is a true picture and we must accept it realistically!

One way out of these difficulties consists of creating such standards for Fellowship as will be universally respected. Since we must start some-

Excerpts from a discussion held at the annual business meeting of The American College of Allergists, Chicago, Illinois, March 21, 1957, Dr. Ethan Allan Brown, presiding.

where, it is proposed to begin by changing the criteria for advancement from Associate Fellow to full Fellowship.

The subject first arose at the Board of Directors meeting held in Boulder, Colorado, in December, 1956. It was felt that the present qualifications for becoming an *Associate Fellow* should not be changed. But, those for becoming a full Fellow should be changed by the addition to the Constitution and Bylaws of one or more qualifying clauses.

It is proposed that these qualifying clauses be made to read, ". . . and, in addition, the Associate Fellow must pass examinations in the various aspects of the subject of allergy as determined by the Board of Examiners of The American College of Allergists.

"Such examinations can be held two days prior to the Annual Congress, or, if necessary, on other dates following due notice published in the ANNALS OF ALLERGY no less than 120 days prior to the date set, whenever the Board of Examiners, with prior approval of the Board of Regents, may decide to change the date. The examination can consist of two written papers of three hours each, and one oral examination of not less than thirty minutes, to be given by two Examiners.

"The Board of Examiners is to consist of any three to six past-presidents of the College as chosen by the Board of Regents.

"A candidate who does not pass the examination may return for re-examination on two successive occasions."

It is planned that the first of these examinations for Fellowship be held in April, 1958, and yearly thereafter. It is also proposed that there be a moderate fee for examination, payable to The American College of Allergists, and that there be a second fee for each re-examination.

It may be that present Associate Fellows will desire to remain indefinitely in the status of Associates. That is their privilege. For those who wish to advance to Fellowship, assurance may be given that they will receive fair treatment, and that all Associate Fellows who possess the qualifications and can pass the examinations undoubtedly will achieve Fellowship.

Such Associate Fellows can also be assured that future postgraduate instructional courses will be directed toward giving *them* ample instruction in the knowledge necessary to pass the examinations. Anyone who has studiously attended several such courses, both preliminary and advanced, will undoubtedly be prepared, especially if this background is bolstered with a knowledge of the fundamentals of the subject matter of allergy as covered both by standard texts and by the material reviewed in the Progress Notes published in the ANNALS OF ALLERGY for the previous three or four years.

The fact that examinations will be held may possibly deter some physicians from joining the College as Associate Fellows because they think that they may not, or cannot, pass the examinations for Fellowship. This

issue must be faced if and when it occurs. It is anticipated, however, that after several years there will be an increase in the quality, and probably in the number, of applicants for Associate Fellowship, since Fellowship in The American College of Allergists will carry ever-increasing prestige and be more meaningful for both present and future Fellows. Present Fellows should urge their Associates to take the examinations as soon as they are eligible.

Dr. Lawrence J. Halpin then discussed the motion in further detail. Additional discussion proved that it was the intention of the attending Fellows that physicians otherwise qualified for Fellowship and at present sub-certified be accepted for full Fellowship without examination.

A motion embodying the above discussion was made, seconded and voted upon affirmatively.

The exact wording of the necessary changes in the Constitution and Bylaws was delegated to the proper committee and as soon as passed upon by legal counsel will be published in a future issue of the ANNALS OF ALLERGY.

# In Memoriam

## RICHARD GILLESPIE HAMILTON

Richard Gillespie Hamilton, M.D., aged forty-eight years, died suddenly May 22, 1957, at 8:00 p.m. at his residence, Fairway Lane, Fox Chapel, Pennsylvania.

He was born in Roswell, New Mexico, son of the late Alma Ritchey and James C. Hamilton. He graduated from the University of Pittsburgh with the degree of B.S. in 1931 and from the University of Pittsburgh School of Medicine with the degree of M.D. in 1933. He was married in April, 1941, to Betty Walton, who with their two sons, Richard Scott and Thomas Walton, survive him. He is also survived by his sisters, Mrs. Verne Wright and Mrs. Joseph Benkert, and a brother, Robert K. Hamilton.

Dr. Hamilton was a member of the Fox Chapel Presbyterian Church, University Club, Fox Chapel Golf Club, and the Rolling Rock Club. He was an associate professor of rhinolaryngology at the University of Pittsburgh, and a member of the American Medical Association, Allegheny County Medical Society, American Academy of Ophthalmology and Otolaryngology, Pittsburgh Allergy Society, Pittsburgh Academy of Medicine, Minute Men of the University of Pittsburgh Medical School, and the American Society of Ophthalmology and Otolaryngology.

He became a Fellow of The American College of Allergists in 1943. He was a diplomate of the American Board of Otolaryngology. He was a member of the board of directors of the Pennsylvania Academy of Ophthalmology and Otolaryngology and of the American College of Surgeons. He was an active staff member of the Eye and Ear Hospital, St. Francis General Hospital, and Magee Hospital.

# Papers of Interest

**Bacon, Catherine, L.:** The role of aggression in the asthmatic attack. Psychoanalyt. Quart., 25:309-324, 1956.

Just as the allergic asthmatic attack is a response to physiologic irritation of the respiratory tract, neurotically-determined asthma may be a response to unconscious fears of assault upon the respiratory apparatus, and the physiologic changes that accompany it are attempts to ward off that assault. Analysis of six asthmatic patients showed that each attack of asthma was preceded by "excretory defiance directed against one or the other parent or a parental image, when the patient was unsuccessfully but aggressively fighting parental domination."

Rees, Linford: Psychosomatic aspects of asthma in elderly patients. J. Psychosom. Res., 1:212-218, 1956.

If emotional difficulties can be treated, the treatment might alleviate attacks brought about by the summative effects of psychologic with infective or allergic factors.

Committee on Advertising: Sedative-hypnotic drugs—chloral hydrate. New England J. Med., 255:706 (Oct.) 1956.

Chloral hydrate has long been and still is one of the most effective and least expensive of the sedative-hypnotic drugs.

Woodward, Doris J., and Solomon, James D.: Fatal agranulocytosis occurring during promazine (Sparine) therapy. J.A.M.A., 162:1308 (Dec.) 1956.

A fatal case of agranulocytosis occurred in a patient on the forty-eighth day of administration of promazine (Sparine). The dosage had been instituted at 100 mg per day and reached a maximum of 1 gm per day in four divided doses over a forty-two-day period.

Tilley, Robert F.: Contact dermatitis from chlorpromazine hydrochloride. New England J. Med., 225:1046 (Nov.) 1956.

Patch tests positive in twenty-seven of ninety-one subjects handling the drug. Contact dermatitis occurred in eight.

Brown, E. E.: Infectious origin of juvenile diabetes. Arch. Pediat., 73:191-198 (June) 1956.

Control of childhood infections, especially chronic sinusitis, is necessary to prevent development of juvenile diabetes, as deduced from chronologic sequence in two patients.

Markow, H.: Allergy, infection, or both? New York State J. Med., 56:1454 (May) 1956.

Gross appearance of nasal secretions is no indication of character of pathologic process. Cytologic study of secretions is suggested as a diagnostic aid and therapeutic guide.

Strang, C.: The fate of children with bronchiectasis. Ann. Int. Med., 44:630-656 (Apr.) 1956.

A study of 119 girls and ninety boys, all under fifteen years of age proved bronchiectasis related to acute respiratory-tract infection especially of the sinuses. Of these, ninety-seven have been followed for six years; with thirty-four completely free of chest symptoms, thirty-eight greatly improved, fourteen slight improved and eleven not improved as result of surgery.

Sanyal, R. K., and West, G. B.: Binding of histamine in mammalian tissues. Nature, 178:1293 (Dec. 8) 1956.

A complex formed *in vitro* contains same proportions of histamine and heparin as found in extracts of mast cells.

Tebrock, H. E., Armino, J. J., and Jonston, J. H.: Usefulness of bioflavonoids and ascorbic acid in treatment of common cold. J.A.M.A., 162:1227 (Nov. 24) 1956.

No effect.

Franz, W. L.; Sands, G. W.; and Heyl, W. L.: Blood ascorbic acid level in bioflavonoid and ascorbic acid therapy of common cold. J.A.M.A., 162:1224 (Nov. 24) 1956.

No effects of bioflavonoids on incidence, duration, "cure" or ascorbic acid blood levels.

Nagy, E., and Kocsar, L.: Experiments on the antihistaminic action of atabrine. Derm. Wschr., 133:265-9, 1956.

Interesting. Worth remembering for future reference.

Woodbridge, R. L.; Grayston, J. T.; Whiteside, J. E.; Loosli, C. G.; Friedman, M.; and Pierce, W. D.: Studies on acute respiratory illness in adenoviruses (APC-RI) J. Infect. Dis., 99:182 (Sept.-Oct.) 1956.

Based upon an antibody titer rise up to 40 per cent, it is suggested that the adenoviruses and B-hemolytic streptococci are associated with respiratory tract illnesses in the majority of affected naval personnel.

## PAPERS OF INTEREST

Balkin, S. S.: Bronchopneumonia, empyema, pneumothorax, and bacteremia due to Salmonella choleraesuis (var. Kunzendorf) treated with chloramphenicol. Am. J. Med., 21:974, 1956.

Successful treatment with Chloromycetin, 4 to 6 gms. daily for a total dose of 292 gms.

Cass, L. J., and Frederik, W. S.: Quantitative comparison of cough-suppressing effects of Romilar and other antitussives. J. Lab. & Clin. Med., 48:879, 1956.

On the basis of a statistical study, dextromethorphan hydrobromide (Romilar) and codeine sulfate are of equal antitussive effectiveness.

Daynes, G.: Bread and Tears—naughtiness, depression and fits due to wheat sensitivity. Proc. Roy. Soc. Med., 49:391-394, 1956.

The author describes a "headache/insomnia/depression syndrome" occurring in adults and similar to the pre-celiac syndrome in children. These symptoms occurred two to fourteen days after the onset of an acute infection. A gluten-free diet promptly relieved all symptoms.

Fischer, H. K., and Dlin, B. M.: The dynamics of placebo therapy: A clinical study. Am. J. Med. Sc., 232:504, 1956.

Three groups of patients were respectively treated with a drug alternating with a placebo; and with psychotherapy alone. The best results were achieved with psychotherapy.

Wintrobe, M. M., and Cartwright, G. E.: Blood disorders caused by drug sensitivity. Arch. Int. Med., 96:559, 1956.

An excellent review of the subject, which should be read by all allergists interested in drugs and their untoward reactions.

Rovito, J.: Non-specific therapy in allergy: A follow-up report. Clin. Med., 3:1059-1064, 1956.

In 1955, the author reported on twelve patients treated with Anergex, an extract of Toxicodendron quercifolia. All of those improved promptly or had complete relief of symptoms after the initial course of injections. The present series concerns patients suffering from ragweed pollen hay fever, pemphigus, "eczema", milk and cheese allergy, asthma due to food allergy, and other disorders almost entirely "cured" following five or more injections. The relief is said to last at least eighteen months. No reactions or side effects have been seen.

Seiden, G. E., and Wurzel, H. A.: Idiopathic benign hyperglobulinemic purpura. New England J. Med., 255:170-172, 1956.

A presentation of the second case reported in the United States. Studies demonstrated a nonspecific perivasculitis. The patient has remained well for five years.

Barefoot, S. W.: The common-sense management of atopic eczema. North Carolina M. J., 16:475-478, 1955.

The author suggests that "any rewarding therapeutic regimen" must take into consideration personality and emotional factors. He classifies his patients as either hyperemotional dependents who must be taught self-confidence and assurance, or psychopathic introverts who must be taught to see the need for emotional dependence. The treatment otherwise consists of a mixture of chloral hydrate and Elixir of Benadryl with local and other systemic medications.

Rubinstein, H. M., and Oliner, L.: Myxedema induced by prolonged iodine administration. New England J. Med., 256:47-52, 1957.

A review of five cases described by Bell in which goiter and myxedema followed administration of potassium iodine, and of Morgan's and Trotter's two carefully studied cases. The authors add a carefully documented case of myxedema in an asthmatic patient who took iodines for six years.

Maganzini, H. C.: Anaphylactoid reaction to penicillins V and G administered orally. New England J. Med., 256:52-56, 1957.

Brief review of the subject and report of two cases. The first responded with a constitutional reaction to one capsule of 400,000 units of penicillin V. The second patient, a fifty-seven-year-old female, responded with sneezing, followed by cyanosis and coma twenty-five minutes following the ingestion of one tablet containing 200,000 units of penicillin G. Thirteen similar cases have been reported, and also one death due to oral penicillin anaphylaxis.

Gaillard, R. A.: Antihistaminic therapy for gingival hyperplasia due to Dilantin. New England J. Med., 256:76-77, 1957.

A report of two cases of gingival hyperplasia which responded successfully to chlorprophenpyridamine maleate (Teldrin Spansule capsules).

Larsen, V.: Some eye changes originating during treatment with ACTH. Ugesk. f. laeger, 118:807-809 (July 12) 1956 (In Danish).

The author describes changes in the retina and of refraction in patients on ACTH therapy and recommends that such patients have regular ophthalmologic examination.

# News Items

## POSTGRADUATE COURSES ON DISEASES OF THE CHEST

The Council on Postgraduate Medical Education of the American College of Chest Physicians will present the following postgraduate courses on Diseases of the Chest this fall:

*12th Annual Postgraduate Course*
Hotel Knickerbocker, Chicago, Illinois
October 21-25, 1957

*10th Annual Postgraduate Course*
Park-Sheraton Hotel, New York City
November 11-15, 1957

*3rd Annual Postgraduate Course*
Ambassador Hotel, Los Angeles, California
December 9-13, 1957

Tuition for each course is $75. The most recent advances in the diagnosis and treatment of chest diseases—medical and surgical—will be presented.

Further information may be obtained by writing to the Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

## POSTGRADUATE COURSE IN ALLERGY

A Postgraduate Course in Allergy will be held at the Albert Einstein Medical Center, Philadelphia 41, Pennsylvania, beginning October 24, 1957. The course will consist of a total of thirty-six hours of instruction divided into twelve sessions of three hours each. The sessions will be held on consecutive Thursdays from 2 to 5 P.M. The fee for the course is $60.00. Registration closes on October 14, 1957.

## WOMEN'S AUXILIARY ANNOUNCES TWO AWARDS

The Women's Auxiliary of The American College of Allergists announces that for presentations at the Fourteenth Annual Meeting of the College two prizes will be awarded.

The Bela Schick Award, a prize of $150 and a Certificate of Award, will be made for the best paper written by an Associate Fellow of The American College of Allergists for presentation at the annual convention of the College.

The Clemens Von Pirquet Award will be made for the best paper written by an intern or resident on any aspect of allergy. This paper will also be presented at the annual convention of the College, and a Certificate of Award will be made and a prize of $75 given to defray traveling expenses to the convention.

All papers are to be judged by a committee consisting of the Program Committee of the Fourteenth Annual Meeting and of members of the Editorial Board of the ANNALS OF ALLERGY. Awards and checks will be presented at the annual meeting in Atlantic City next April.

## MISSISSIPPI VALLEY CONTEST WINNERS ANNOUNCED

It was recently announced that Dr. Ethan Allan Brown, for the second time in succession, won the second place in the Mississippi Valley Medical Society Essay Contest with a paper entitled "The Pulmonary Cripple." First place was won by Dr. Wilfred Dorfman, whose entry was entitled "The Challenge of the New Drugs." Dr. Dorfman is a member of the Executive Committee of the Academy of Psychosomatic Medicine, of which Dr. Brown is President.

## ALLERGY SOCIETY OF THE DISTRICT OF COLUMBIA

The founding meeting of the Allergy Society of the District of Columbia was held on May 22, 1957. The following officers were elected:

President—Alvin Seltzer, M.D.
Vice President—Ellis April, M.D.
Secretary-Treasurer—Marvin Fuchs, M.D.

Appointed to the Executive Committee were Harry S. Bernton, M.D., and William A. Howard, M.D.

## CANADIAN ACADEMY OF ALLERGY

The newly elected officers of the Canadian Academy of Allergy for 1957-58 are:

President—T. M. Sieniewicz, Halifax, Nova Scotia
Vice President—J. D. L. FitsGerald, Toronto, Ontario
Secretary-Treasurer—J. Leger, Montreal, Quebec

## NEW JERSEY ALLERGY SOCIETY

The newly elected officers of the New Jersey Allergy Society for 1957-58 are:

President—Harry Hershey, M.D., Jersey City, New Jersey
Vice President—Frank H. Feldman, M.D., Newark, New Jersey
Secretary—Joseph Jehl, M.D., Clifton, New Jersey
Treasurer—Francis Pflum, M.D., Asbury Park, New Jersey

## WASHINGTON STATE SOCIETY OF ALLERGY

The Washington State Society of Allergy had an all-day meeting on Saturday, May 4, 1957, at Hotel Chinook in Yakima, Washington.

New officers are:

President—Lois Frayser, M.D., Seattle, Washington
Vice President—James E. Stroh, M.D., Seattle, Washington
Secretary-Treasurer—Dr. Herbert L. Cahn, M.D., Richland, Washington

## WEST VIRGINIA STATE SOCIETY OF ALLERGY

The West Virginia State Society of Allergy has been founded. The current officers are as follows:

President—Merle S. Scherr, M.D., Charleston, West Virginia
Vice President—John A. B. Holt, M.D., Charleston, West Virginia
Secretary-Treasurer—Marshall J. Carper, M.D., Charleston, West Virginia

## CHICAGO SOCIETY OF ALLERGY

The new officers of the Chicago Society of Allergy for 1957-1958 are:

President—Norman J. Ehrlich, M.D.
President-Elect—Harold C. Wagner, M.D.
Secretary-Treasurer—Israel A. Fond, M.D.

## I.A.A. CONGRESS PAPERS

It is announced for the second time that those who wish to present previously unpublished papers at the International Association of Allergologists meeting in Paris, France, during the week of October 19-26, 1958, should send the title and a 200-word abstract, typed double-space, in triplicate on thin paper, to Dr. S. M. Feinberg, President, I.A.A., 303 E. Chicago Avenue, Chicago 11, Illinois (for Americans), or to Dr. B. N. Halpern, Chairman of Organizing Committee, 197 Boulevard St. Germain, Paris, vii, France (for others).

The registration fee is $32.00 for physicians and $15 for their wives and guests.

# BOOK REVIEW

THE AMERICAN FLUORIDATION EXPERIMENT. F. B. Exner, M.D., and G. L. Waldbott, M.D. 277 pages, including index. New York: The Devin-Adair Company, 1957. Price $3.75.

Bertrand Russell once observed that righteous indignation was one of the least trustworthy of the emotions. If the case the authors present has any merit, they so overwhelm the reader with their shouting that he cannot hear what they say about it.

In general (page 46) it is said, "fluoridation violates the most sacred laws of God and man."

In particular, if the reader refuses to fall into this trap, he is told that fluoridation does not work especially on the teeth and that, if it does work, it causes a multitude of vague disorders few physicians have seen or described. In any case, if it did work to harden the teeth it is only effective in children up to the age of eight and should not, therefore, be given to the rest of the population. The children who would supposedly benefit should receive tablets or fluoridated water in measured quantities on a voluntary or free public health service.

Not content with a simple exposition, the authors use every emotionally tinged word and work themselves up into a fierce, hysterical lather. The introduction is entitled "Twenty-Eight Million Human Guinea Pigs." The program is described as "a huge, unprecedented and possibly disastrous experiment." The United States Public Health Service has "ventured to use public water systems as a vehicle for the random treatment of whole populations with a dangerous drug known to be cumulatively poisonous when consumed in minute quantities."

The American Dental Association has "suddenly turned its face away from the admitted prime cause of tooth decay (carbohydrate ingestion) and chosen instead to promote a program of mass medication of dubious effect and even more dubious safety."

"The most alarming aspect of the fluoridation program is the reckless arrogance, obstinacy and unscrupulousness of the United States Public Health Service in continuing to promote the program while ignoring and, where possible, suppressing evidence that it is neither safe nor generally efficacious."

". . . the slender scientific base on which the vast inverted pyramid of fluoridation is reared has been shown to consist of inadequate, contradictory and discredited epidemiological studies, biased and selective reviews of the literature, distorted interpretations of the Public Health Service's own findings and a few laboratory and clinical studies which have been repeatedly discredited by subsequent investigation."

"Why, then, do they (the Public Health Service) not act? Are they waiting for a face-saving alternative that will permit the gradual abandonment of water fluoridation, while diverting attention from their own criminal responsibility for endangering the health of millions? Or are they so enslaved and paralyzed by past ideological and personal commitments that they will do nothing to rescue themselves and the nation from the trap into which their arrogant folly has precipitated us?"

Those who agree with the authors are "honest and scientifically respectable" but they are ". . . excoriated unmercifully . . . for being too honest."

Those who disagree have "joined the parade." Of them . . . "it is hard to tell where stupidity and carelessness leave off and dishonesty begins."

"It is hard to tell the schemer from the weak and venal tool."

These labels are applied to Thomas J. Hill, Chairman of the Council on Dental

Research of the American Dental Association; Francis A. Arnold, Director of the National Institute of Dental Research; Detler W. Bronk, President of the National Academy of Science, and John W. Knudson, President of the American Public Health Association. The Board of Trustees of the American Medical Association has endorsed the principle of fluoridation.

According to present statistics, 1,437 communities with a combined population of 30,500,000 have fluoridated their water supplies and approximately 100 have ceased or abandoned the procedure. Hearings are in progress for fluoridation of the water supplies of New York and other large cities.

Whatever arguments the authors may have on their side, they have obscured them with specious, special pleadings and the techniques of obvious propaganda. As a result, the book fails in its purpose and becomes rather dull.

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Rosenau and Anderson established the fact that between the time of sensitization of the guinea-pig and the time when the animal is ripe for reaction to a second injection there should elapse an incubation period of ten days. They saw that in order to sensitize the guinea-pig a minimum dose of serum (one-millionth of a cubic centimeter) was sufficient, and that once the state of hypersensitiveness was established it was capable of lasting for months.—DR. A. BESREDKA, Anaphylaxis and Anti-Anaphylaxis and Their Experimental Foundations, 1919.